World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Alcoholic drinks
and the risk of cancer

2018

World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund
世界癌症研究基金會

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WORLD CANCER RESEARCH FUND NETWORK

Our Vision

We want to live in a world where no one develops a preventable cancer.

Our Mission

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

Our Network

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

Our Continuous Update Project (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see inside back cover).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Alcoholic drinks and the risk of cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see dietandcancerreport.org

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

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Key

See **Glossary** for definitions of terms highlighted in *italics*.

References to other parts of the Third Expert Report are highlighted in purple.

Executive summary

Background and context

In this part of the Third Expert Report from our Continuous Update Project (CUP) – the world's largest source of scientific research on cancer prevention and survivorship through diet, nutrition and physical activity – we analyse global research on how consuming alcoholic drinks affects the risk of developing cancer.[1] This includes new studies as well as those included in the 2007 Second Expert Report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective [1].

Alcohol is the common term for ethanol, which is produced when sugars are broken down by yeasts to release *energy*. This process, known as fermentation, is used to produce alcoholic drinks, such as beers (typically three to seven per cent alcohol by volume), wines (typically nine to 15 per cent alcohol by volume) and spirits (typically 35 to 50 per cent alcohol by volume). Most alcoholic drinks are manufactured industrially.

Alcohol (ethanol) is a source of dietary energy, providing 7 kilocalories per gram. It also acts as a drug, affecting both mental and physical responses.

Worldwide consumption of alcoholic drinks in 2016 was equal to 6.4 litres of pure alcohol (ethanol) per person aged 15 years or older, which is equivalent to about one alcoholic drink per day. However, consumption varies widely.

In many countries, alcohol consumption is a public health problem. Alcohol consumption is expected to continue to rise in half of the World Health Organization (WHO) regions unless effective *policy* reverses the trend [2].

Alcohol drinking may also be associated with other behaviours such as tobacco smoking. In addition, self-reporting of levels of alcohol intake is liable to underestimate consumption, sometimes grossly.

Harmful alcohol consumption has been linked to more than 200 diseases and injury conditions, including *cirrhosis*, infectious diseases, cardiovascular disease and early dementia [2].

How the research was conducted

The global scientific research on diet, nutrition, physical activity and the risk of cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists to draw conclusions about which factors increase or decrease the risk of developing the disease (see Judging the evidence).

This Third Expert Report presents in detail findings for which the Panel considered the evidence strong enough to make Cancer Prevention Recommendations (where appropriate) and highlights areas where more research is required (where the evidence is suggestive of a causal or protective relationship but is limited in terms of amount or by methodological flaws). Evidence that was considered by the Panel but was too limited to draw firm conclusions is not covered in detail in this Third Expert Report.

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin.

Findings

There is **strong evidence** that consuming:

- **alcoholic drinks increases** the risk of cancers of the mouth, pharynx and larynx; oesophagus (*squamous cell carcinoma*) and breast (pre and postmenopause)
- **two or more alcoholic drinks a day** (about 30 grams or more of alcohol per day) **increases** the risk of colorectal cancer
- **three or more alcoholic drinks a day** (about 45 grams or more of alcohol per day) **increases** the risk of stomach and liver cancers
- **up to two alcoholic drinks a day** (up to about 30 grams of alcohol per day) **decreases** the risk of kidney cancer.

The evidence shows that, in general, the more alcoholic drinks people consume, the higher the risk of many cancers. The exception is kidney cancer, where the risk is lower for up to two alcoholic drinks a day; however, for more than two drinks a day the level of risk is unclear. For some cancers, there is an increased risk with any amount of alcohol consumed, whereas for other cancers the risk becomes apparent from a higher level of consumption, of about two or three drinks a day (about 30 or 45 grams of alcohol per day).

The Panel used this strong evidence when making Recommendations (see below) designed to reduce the risk of developing cancer.

There is also other evidence on alcoholic drinks that is limited (either in amount or by methodological flaws), but is suggestive of an increased risk of lung, pancreatic and skin cancers. Further research is required, and the Panel has not used this evidence to make recommendations.

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. For cancer prevention it's best not to drink alcohol. For people who choose to drink alcohol, the advice is to follow your national guidelines. The Recommendations are listed on the inside back cover.

References

[1] World Cancer Research Fund/American Institute for Cancer Research, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007. Available from wcrf.org/about-the-report

[2] WHO. Global status report on alcohol and health 2014. 2014. World Health Organization. Accessed 16/06/2017; available from http://www.who.int/substance_abuse/publications/global_alcohol_report

1. Alcoholic drinks and the risk of cancer: a summary matrix

ALCOHOLIC DRINKS AND THE RISK OF CANCER					
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Alcoholic drinks[1]	Mouth, pharynx and larynx 2018 Oesophagus (*squamous cell carcinoma*) 2016 Liver 2015[2] Colorectum 2017[3] Breast (postmenopause) 2017[4]
	Probable	Alcoholic drinks	Kidney 2015[5]	Alcoholic drinks	Stomach 2016[2] Breast (premenopause) 2017[4]
LIMITED EVIDENCE	Limited – suggestive			Alcoholic drinks	Lung 2017 Pancreas 2012[2] Skin (*basal cell carcinoma* and malignant *melanoma*) 2017
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

1 Alcoholic drinks include beers, wines, spirits, fermented milks, mead and cider. The consumption of alcoholic drinks is graded by the International Agency for Research on Cancer as carcinogenic to humans (Group 1)[3].

2 The conclusions for alcoholic drinks and cancers of the liver, stomach and pancreas were based on evidence for alcohol intakes above approximately 45 grams of ethanol per day (about three drinks a day). No conclusions were possible for these cancers based on intakes below 45 grams of ethanol per day.

3 The conclusion for alcoholic drinks and colorectal cancer was based on alcohol intakes above approximately 30 grams of ethanol per day (about two drinks a day). No conclusion was possible based on intakes below 30 grams of ethanol per day.

4 No threshold level of alcohol intake was identified in the evidence for alcoholic drinks and breast cancer (pre and postmenopause).

5 The conclusion for alcoholic drinks and kidney cancer was based on alcohol intakes up to approximately 30 grams of ethanol per day (about two drinks a day). There was insufficient evidence to draw a conclusion for intakes above 30 grams of ethanol per day.

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from nasopharynx, cervix and skin, where the year given is the year the systematic literature review was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

Definitions of World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria

'Strong evidence': Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship and generally justifies making public health recommendations.

'Convincing': Evidence is strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

'Probable': Evidence is strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies making recommendations designed to reduce the risk of cancer.

'Limited evidence': Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations.

'Limited – suggestive': Evidence is inadequate to permit a judgement of a probable or convincing causal (or protective) relationship, but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement generally does not justify making recommendations.

'Limited – no conclusion': There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these. Evidence that was judged to be 'limited – no conclusion' is mentioned in Evidence and judgements (**Section 5**).

'Substantial effect on risk unlikely': Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet, nutrition, body fatness or physical activity is unlikely to have a substantial causal (or protective) relation to a cancer outcome.

For further information and to see the full grading criteria agreed by the Panel to support the judgements shown in the matrices, please see **Appendix 1**.

The next section describes which evidence the Panel used when making Recommendations.

2. Summary of Panel judgements

The conclusions drawn by the Continuous Update Project (CUP) Panel are based on the evidence from both epidemiological and mechanistic studies relating specific alcoholic drinks to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between alcoholic drinks and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The CUP Panel concluded:

STRONG EVIDENCE

Convincing

- **Increased risk**
  - Consumption of alcoholic drinks[1] is a convincing cause of cancers of the mouth, pharynx and larynx; oesophagus (*squamous cell carcinoma*); liver;[2] colorectum;[3] and breast (postmenopause).[4]

Probable

- **Decreased risk**
  - Consumption of alcoholic drinks[1] probably protects against kidney cancer.[5]
- **Increased risk**
  - Consumption of alcoholic drinks[1] is probably a cause of stomach cancer[2] and premenopausal breast cancer.[4]

The evidence shows that, in general, the more alcoholic drinks people consume, the higher the risk of many cancers. The exception is kidney cancer, where the risk is lower for up to two alcoholic drinks a day; however, for more than two drinks a day the level of risk is unclear. For some cancers, there is an increased risk with any amount of alcohol consumed, whereas for other cancers the risk becomes apparent from a higher level of consumption, of about two or three drinks a day (30 or 45 grams of alcohol per day).

The Panel has used this strong evidence when making Recommendations designed to reduce the risk of developing cancer (see Recommendations and public health and policy implications, Section 2: Recommendations for Cancer Prevention).

LIMITED EVIDENCE

Limited – suggestive

- **Increased risk**
  - The evidence suggesting that consumption of alcoholic drinks[1] increases the risk of cancers of the following types is limited: lung, pancreas[2] and skin (*basal cell carcinoma* and malignant *melanoma*).

[1] Alcoholic drinks include beers, wines, spirits, fermented milks, mead and cider. The consumption of alcoholic drinks is graded by the International Agency for Research on Cancer as carcinogenic to humans (Group 1) [3].

[2] The conclusions for alcoholic drinks and cancers of the liver, stomach and pancreas were based on evidence for alcohol intakes above approximately 45 grams of ethanol per day (about three drinks a day). No conclusions were possible for these cancers based on intakes below 45 grams of ethanol per day.

[3] The conclusion for alcoholic drinks and colorectal cancer was based on alcohol intakes above approximately 30 grams of ethanol per day (about two drinks a day). No conclusion was possible based on intakes below 30 grams of ethanol per day.

[4] No threshold level of alcohol intake was identified in the evidence for alcoholic drinks and breast cancer (pre and postmenopause).

[5] The conclusion for alcoholic drinks and kidney cancer was based on alcohol intakes up to 30 grams of ethanol per day (about two drinks a day). There was insufficient evidence to draw a conclusion for intakes above approximately 30 grams of ethanol per day.

The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

See Definitions of WCRF/AICR grading criteria (**Section 1**: Alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'strong evidence', 'convincing', 'probable', 'limited evidence' and 'limited – suggestive'.

3. Definitions and patterns

3.1 Alcoholic drinks

3.1.1 Definitions and sources

Alcohols are a group of organic compounds in which one of the hydrogen atoms is replaced by a functional hydroxyl group. Among this family of compounds is ethanol, which is commonly known as alcohol, or drinking alcohol. In this Third Expert Report, the term 'alcohol' refers specifically to ethanol, and the term 'alcoholic drinks' refers to drinks containing ethanol.

Alcohol is produced in nature when sugars are broken down by yeasts to release *energy*. This process of fermentation is used to produce alcoholic drinks. Alcohol is a source of dietary energy. It also acts as a drug, affecting both mental and physical responses.

Alcoholic drinks include beers, wines and spirits. Other alcoholic drinks that may be locally important include fermented milks, mead (fermented honey-water) and cider (fermented apples).

Most alcoholic drinks are manufactured industrially. Some are made domestically or illegally and may be known as 'moonshine' or 'hooch'. For general information about alcohol composition and consumption patterns, see **Box 1**.

Box 1: Alcoholic drinks – composition and consumption patterns

3.1.2 Composition

Ethanol has an *energy* content of 7 kilocalories per gram and is metabolised by the liver. On average, blood alcohol levels reach a maximum between 30 and 60 minutes after drinking an alcoholic drink, and the body can metabolise 10 to 15 grams of ethanol per hour.

Alcohol alters the way the central nervous system functions. Very high alcohol consumption (where blood alcohol reaches 0.4 per cent) can be fatal, as can long-term, regular, high intakes.

3.1.3 Consumption patterns

Much of the data on average consumption of alcoholic drinks, internationally and nationally, are not informative. Consumption varies widely within and between populations, usually as a function of availability, price, culture or religion, and dependency. In the past, women were less likely to drink alcohol than men, but gender differences are declining, particularly in younger age groups [4]. In countries where considerable amounts of alcoholic drinks are produced domestically and by artisanal methods, overall consumption will most likely be underestimated.

In many countries, alcohol consumption is a public health problem. Alcohol consumption is expected to continue to rise in half of the World Health Organization (WHO) regions unless effective *policy* reverses the trend [2].

Worldwide average consumption in 2016 was equal to 6.4 litres of ethanol per person aged 15 years or older, which is equivalent to about one alcoholic drink per day [5]. However, in a 2014 report, 62 per cent of the population surveyed had not consumed alcohol in the past year, and 14 per cent had consumed alcohol earlier in life but not in the past 12 months [2]. Almost half of the global adult population (48 per cent) has never consumed alcohol [2].

The data for 2016 show that countries in Eastern Europe have the highest average alcohol intakes (see **Table 3.1**) [5]. The figures are averaged over each whole country and include people who do not drink alcohol.

Alcoholic drinks are illegal in Islamic countries. In countries where alcoholic drinks are legal, consumption is often limited to adults, and price may also restrict availability, in particular to young people.

Many countries recommend restriction of alcohol intake for health reasons, although guidance varies from country to country. Some countries, including Spain, Japan and Poland, recommend no more than 40 grams of ethanol a day for men and 20 grams a day for women [6]. Others, for example Finland and Croatia, are more restrictive and recommend no more than 20 grams of ethanol per day for men and 10 grams for women [6]. Others do not differentiate between men and women; for example the UK, the Netherlands and Australia [6].

Despite some possible benefits for ischaemic heart disease and diabetes from consuming low amounts of alcohol, harmful alcohol consumption has been linked to more than 200 diseases and injury conditions [2]. They include *cirrhosis*, infectious diseases, cardiovascular disease, diabetes (consumption of large amounts of alcohol), neuropsychiatric conditions, early dementia and fetal alcohol syndrome [2].

Table 3.1: National per capita consumption of alcohol higher than 12 litres in 2016 [5]

Rank	Country	Alcoholic drinks per day (aged 15 years or older)[1]
1	Lithuania	3.32
2	Belarus	3.00
3	Republic of Moldova	2.90
4	Russian Federation	2.54
5	Romania	2.50
5	Czech Republic	2.50
7	Croatia	2.48
7	Bulgaria	2.48
9	Belgium	2.41
10	Ukraine	2.34
10	Estonia	2.34
12	Slovakia	2.25
12	Poland	2.25
12	Latvia	2.25
12	Hungary	2.25
12	United Kingdom	2.25

3.2 Types of alcoholic drinks

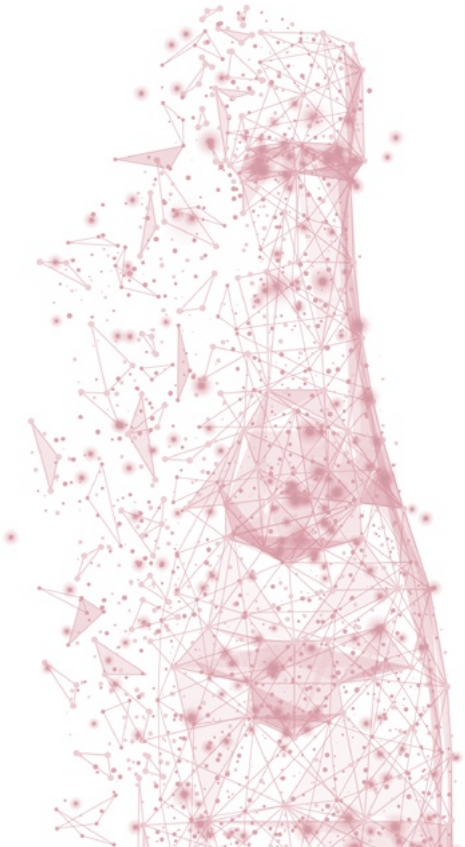
3.2.1 Beers

Beer is traditionally produced from barley; today other cereal grains are also used. The grain starches are converted to sugars and then fermented by yeasts. Beers fall into two categories, ales and lagers, which use different yeasts in the fermentation process. Beer commonly contains between three and seven per cent ethanol by volume, but that figure can be much higher. No-alcohol or low-alcohol beers are also available; most are lagers. Definitions regarding maximum ethanol content for low-alcohol beers vary from country to country. The term 'beer' in this Third Expert Report includes ales and lagers.

There are many varieties of beer, with different compositions. Beers generally contain a variety of bioavailable phenolic and polyphenolic compounds, which contribute to the taste and colour, many of which have *antioxidant* properties. Magnesium, potassium, riboflavin, folate and other B vitamins may also be present in beer.

3.2.2 Wines

Wines are usually produced from grapes, which are crushed to produce juice and must, which is then fermented. Sparkling wines, such as champagne, prosecco and cava, contain a significant amount of carbon dioxide. Different grapes and vinification processes affect the colour and strength of the final product. The alcohol content ranges from about nine to 15 per cent ethanol by volume. Wines may be flavoured with herbs or fortified with spirits to produce drinks of alcohol content between about 16 and 20 per cent ethanol by volume; examples include vermouth, sherry and port. Low-alcohol and alcohol-free wines are also available. Wines can also be produced from fruit other than grapes and from rice (sake). In this Third Expert Report, the term 'wine' means grape wines.



[1] The number of alcoholic drinks per day was estimated from litres of ethanol consumed per person, per year, where one drink is equivalent to 15 grams of ethanol. The figures are averaged over the whole country and include people who do not drink alcohol.

The composition of wine depends on the grape varieties used, as well as the growing conditions and the wine-making methods, which may vary. Red wines contain high levels of phenolic and polyphenolic compounds (up to about 800 to 4,000 milligrams per litre), particularly resveratrol, derived from the grape skins. Like those in beer, these phenolic compounds add taste and colour. White wines contain fewer phenolics. Red wine has been shown to have *antioxidant* activity in laboratory experiments. Wine also contains sugars (mainly glucose and fructose), volatile acids (mainly acetic acid), carboxylic acids, and varying levels of *calcium*, copper, iron, magnesium, potassium, and vitamins B1, B2 and B6 may be present.

3.2.3 Spirits

Spirits are usually produced from cereal grains and sometimes from other fermented plant foods. They are distilled, to produce drinks with a higher concentration of alcohol than either beers or wines. Distilled drinks may have herbs and other ingredients added to give them their distinctive character.

Some of the most globally familiar spirits are brandy (distilled wine), whisky and gin (distilled from grains), rum (from molasses), aguardiente – also known as cachaça – (from sugar cane), vodka (from grain or from potatoes) and tequila and mescal (from agave and cactus plants). Spirits and liqueurs can also be made from fruit.

The alcohol content of spirits and liqueurs is usually between 35 and 50 per cent ethanol by volume but can be even higher.

4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence in the CUP see Judging the evidence.

'Relative risk' (RR) is used in this Third Expert Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios' and *'odds ratios'*.

4.2 Specific

Specific factors that the Panel bears in mind when interpreting evidence on whether consuming alcoholic drinks increases or decreases the risk of developing cancer are described in this section. Factors that are relevant to specific cancers are presented here too.

4.2.1 Alcoholic drinks

Definitions. Alcoholic drinks include beers, wines and spirits (see **Section 3.1.1**). Ethanol (also referred to in this Third Expert Report as 'alcohol') is the active ingredient in alcoholic drinks; the concentration varies, depending on the type of drink. The main alcoholic drinks consumed, in ascending order of ethanol content, are beers and ciders; wines; wines 'fortified' with spirits; and spirits and liqueurs.

Most studies report overall alcohol consumption across all types of drinks. Some studies also report analyses stratified by type of drink. Both types of analyses are included in the CUP.

Confounding. The effects of alcohol are heavily confounded by other behaviours such as smoking tobacco. Tobacco smoking is a potential *confounder* especially for smoking-related cancers including oral cancers,

including those of the mouth, pharynx and larynx; and cancers of the oesophagus and lung [7]. The risk of developing cancers of the mouth, pharynx and larynx and oesophagus has been shown to be amplified if people who drink also smoke tobacco, and if people who smoke tobacco also drink alcohol [8, 9].

Measurement. In recent years, the strength and serving size of some alcoholic drinks have increased. For example, in the UK, wine is commonly served in 250 millilitre glasses rather than the standard 125 or 175 millilitre glass. In addition, the alcohol content of drinks varies widely. Studies that measure consumption in terms of number of drinks may refer to very different amounts of alcohol (also see **Box 2**).

Generally there are two measures of *exposure*: the number of alcoholic drinks per time period, and ethanol intake in grams or millilitres per time period. The former measure is likely to be less precise because the size and strength of each drink are unknown. In CUP analyses, for studies that reported on number of alcoholic drinks, the intake was rescaled to grams of ethanol per day using 13 grams as the average content of ethanol per one drink or one occasion.

Reporting bias. Self-reporting of levels of alcohol intake is liable to underestimate consumption, sometimes grossly, because alcohol is known to be unhealthy and undesirable, and thus is sometimes consumed secretly. People who consume large amounts of alcohol usually underestimate their consumption, as do those who drink illegal or unregulated alcoholic drinks.

Box 2: Does the type of alcoholic drink matter?

The Panel judges that alcoholic drinks are a cause of various cancers, irrespective of the type of alcoholic drink consumed. The causal factor is evidently the ethanol itself. The extent to which alcoholic drinks are a cause of various cancers depends on the amount and frequency of alcohol consumed.

Epidemiological studies often identify the type of alcoholic drink consumed, and some appear to show that some types of drinks may have different effects. For example, for some cancers of the mouth, pharynx and larynx, a significant increased risk was observed for beer and spirits, whereas no significant association was observed for wine. In these cases, there is a possibility of residual *confounding* effects: people who drink wine in many countries tend to have healthier behaviours than those who drink beer or spirits, and most studies show that all types of alcoholic drinks increase the risk of cancer.

Apparent discrepancies in the strength of evidence may also be due in part to variation in the amounts of different types of alcoholic drinks consumed. In general, the evidence suggests similar effects for different types of alcoholic drinks.

4.2.2 Cancers

The information provided here on 'Other established causes' of cancer is based on judgements made by the International Agency for Research on Cancer (IARC) [10], unless a different reference is given. For more information on findings from the CUP on diet, nutrition, physical activity and the risk of cancer, see other parts of this Third Expert Report.

4.2.2.1 Mouth, pharynx and larynx

Definitions. Organs and tissues in the mouth include the lips, tongue, inside lining of the cheeks (buccal mucosa), floor of the mouth, gums (gingiva), palate and salivary glands. The pharynx (throat) is the muscular cavity leading from the nose and mouth to the larynx (voice box), which includes the vocal cords. Cancers of the mouth, pharynx and larynx are types of head and neck cancer.

Classification. In sections of this Third Expert Report where the evidence for cancers of the mouth, pharynx and larynx is discussed, the term 'head and neck cancer' includes cancers of the mouth, larynx, nasal cavity, salivary glands and pharynx, and the term 'upper aerodigestive tract cancer' includes head and neck cancer together with oesophageal cancer. Nasopharyngeal cancer is reviewed separately from other types of head and neck cancer in the CUP.

Other established causes. Other established causes of cancers of the mouth, pharynx and larynx include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of cancers of the mouth, pharynx and larynx. Chewing betel quid (nuts wrapped in a betel leaf coated with calcium hydroxide), with or without added tobacco, is also a risk factor for cancers of the mouth and pharynx. Smoking tobacco is estimated to account for 42 per cent of deaths from mouth and oropharynx (the part of the throat just behind the mouth) cancers worldwide [11].

Infection

Some human papilloma viruses (HPV) are carcinogenic, and oral infection with these types is a risk factor for mouth, pharynx and larynx cancer. The prevalence of carcinogenic HPV types in oropharyngeal cancer is estimated to be about 70 per cent in Europe and North America [12].

Environmental exposures

Exposure to asbestos increases the risk of laryngeal cancer.

Confounding. Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than people who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects by smoking tobacco; that is, not a direct result of the exposure examined.

For more detailed information on *adjustments* made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.1**).

The characteristics of people developing cancers of the mouth, pharynx and larynx are changing. Increasingly, a large cohort of younger people who are infected with the carcinogenic HPV types 16 or 18, and who do not smoke and do not consume a large amount of alcohol, are now developing these cancers. As far as possible, the conclusions for mouth, pharynx and larynx take account of this changing natural history. However, most published epidemiological studies reviewing diet and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

4.2.2.2 Oesophagus

Definition. The oesophagus is the muscular tube through which food passes from the pharynx to the stomach.

Classification. The oesophagus is lined over most of its length by squamous *epithelial* cells, where *squamous cell carcinomas* arise. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar epithelial cells, from which *adenocarcinomas* arise. The oesophageal-gastric junction and gastric cardia are also lined with columnar epithelial cells.

Globally, squamous cell carcinoma is the most common type and accounts for 87 per cent of cases [13]; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations. Squamous cell carcinomas have different geographic and temporal trends from adenocarcinomas and follow a different disease path. Different approaches or definitions in different studies are potential sources of heterogeneity.

Other established causes. Other established causes of lung cancer include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of oesophageal cancer. *Squamous cell carcinoma* is more strongly associated with smoking tobacco than *adenocarcinoma* [14]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [11].

Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of HPV [15]. Helicobacter pylori infection, an established risk factor for *non-cardia stomach cancer*, is associated with a 41 to 43 per cent decreased risk of oesophageal adenocarcinoma [16, 17].

Other diseases

Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus [14]. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia (in which the valve at the end of the oesophagus called the 'cardia' fails to open and food gets stuck in the oesophagus) [14].

Family history

Tylosis A, a late-onset, inherited *familial* disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of oesophageal squamous cell carcinoma [18].

Confounding. Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in

assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects by smoking tobacco; that is, not a direct result of the *exposure* examined.

For more detailed information on adjustments made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.6**).

4.2.2.3 Lung

Definition. The lungs are part of the respiratory system and lie in the thoracic cavity. Air enters the lungs through the trachea, which divides into two main bronchi, each of which is subdivided into several bronchioles, which terminate in clusters of alveoli.

Classification. The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

NSCLC accounts for 85 to 90 per cent of all cases of lung cancer and has three major subtypes: *squamous cell carcinoma*, *adenocarcinoma* and *large-cell carcinoma*. Adenocarcinoma and squamous cell carcinoma are the most frequent histologic subtypes, accounting for 50 per cent and 30 per cent of NSCLC cases, respectively [19].

SCLC accounts for 10 to 15 per cent of all lung cancers; this form is a distinct pathological entity characterised by aggressive biology, propensity for early *metastasis* and overall poor prognosis.

Other established causes. Other established causes of lung cancer include the following:

Smoking tobacco

Smoking tobacco is the main cause of lung cancer and increases the risk of all the main subtypes. However, *adenocarcinoma* is the most common subtype among those who have never smoked. It is estimated that over 90 per cent of cases among men and over 80 per cent among women worldwide are attributable to smoking tobacco [20]. Passive smoking (inhalation of tobacco smoke from the surrounding air) is also a cause of lung cancer.

Previous lung disease

A history of emphysema, *chronic* bronchitis, tuberculosis or pneumonia is associated with an increased risk of lung cancer [21].

Other exposures

Occupational exposure to asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and some heavy metals is associated with an increased risk of lung cancer [22], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [23].

Confounding. Smoking tobacco is the main cause of lung cancer. People who smoke also tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual *confounding* effects by smoking tobacco; that is, not a direct result of the exposure examined.

However, this evaluation may not completely mitigate the problem. Stratification by smoking status (for example, dividing the study population into people who smoke, those who used to smoke and those who have never smoked) can be useful, but typically the number of lung cancers in people who have never smoked is limited. Moreover, if an association is observed in people who currently smoke but not in people who have never smoked, residual confounding effects in the former group may be an explanation, but it is also plausible that the factor is only operative in ameliorating or enhancing the effects of tobacco smoke.

It is also important to differentiate residual confounding effects from a true effect limited to people who smoke. Because smoking tobacco is such a strong risk factor for lung cancer, residual confounding effects remain a likely explanation, especially when the estimated risks are of moderate magnitudes.

4.2.2.4 Stomach

Infection with *H. pylori* is strongly implicated in the aetiology of intestinal *non-cardia stomach cancer*. The role of any other factor is to enhance risk of infection, integration and/or persistence.

Definition. The stomach is part of the digestive system, located between the oesophagus and the small intestine. It secretes enzymes and gastric acid to aid in food digestion and acts as a receptacle for masticated food, which is sent to the small intestines though muscular contractions.

Classification. Stomach cancer is usually differentiated by the anatomical site of origin: *cardia stomach cancer* (cardia cancer), which occurs near the gastro-oesophageal junction, and *non-cardia stomach cancer* (non-cardia cancer), which occurs outside this area, in the lower portion of the stomach. Cardia and non-cardia stomach cancer have distinct pathogeneses and aetiologies, but not all studies distinguish between them, particularly older studies. For these studies, there is a greater likelihood that the general term 'stomach cancer' may reflect a combination of the two subtypes, and therefore results may be less informative. Furthermore, definitions of cardia cancer classifications sometimes vary according to distance from the gastro-oesophageal junction, raising concerns about misclassification [24].

Other established causes. Other established causes of stomach cancer include the following:

Smoking tobacco

Smoking tobacco is a cause of stomach cancer. It is estimated that 13 per cent of deaths worldwide are attributable to smoking tobacco [11].

Infection

Persistent colonisation of the stomach with *H. pylori* is a risk factor for non-cardia stomach cancer, but in some studies has been found to be inversely associated with the risk of cardia stomach cancer [25, 26].

Industrial chemical exposure

Occupational exposure to dusty and high-temperature environments – as experienced by wood-processing and food-machine operators – has been associated with an increased risk of stomach cancer [27]. Working in other industries, including rubber manufacturing, coal mining, metal processing and chromium production, has also been associated with an elevated risk of this cancer [28, 29].

Family history and ethnicity

Inherited mutations of certain genes, particularly the glutathione S-transferase (GSTM1)-null phenotype, are associated with an increased risk of stomach cancer [30]. Certain *polymorphisms* of interleukin genes (IL-17 and IL-10) have also been associated with increased risk of stomach cancer, particularly in Asian populations. These polymorphisms may interact with *H. pylori* infection [31] and smoking tobacco [32] to affect cancer risk.

Pernicious anaemia

People with the autoimmune form of pernicious anaemia have an increased risk of stomach cancer [33, 34]. This form of pernicious anaemia involves the autoimmune destruction of parietal cells in the gastric mucosa [34, 35]. These cells produce intrinsic factor, a protein

that is needed to absorb vitamin B12 from foods, so the resultant vitamin B12 deficiency hinders the production of fully functioning red blood cells.

Confounding. Smoking tobacco and *H. pylori* infection are possible *confounders* or *effect modifiers*.

For more detailed information on adjustments made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.3**).

4.2.2.5 Pancreas

Definition. The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, *exocrine* and *endocrine*. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas produce *hormones* including insulin and glucagon, which influence glucose metabolism.

Classification. Over 95 per cent of pancreatic cancers are *adenocarcinomas* of the exocrine pancreas, the type included in the CUP.

Other established causes. Other established causes of pancreatic cancer include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is an established cause of pancreatic cancer, and approximately 22 per cent of deaths from pancreatic cancer are attributable to smoking tobacco [11].

Family history

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited mutations), although a family history increases risk, particularly where more than one family member is involved [36].

Confounding. Smoking tobacco is a possible *confounder*.

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed.

4.2.2.6 Liver

Definition. The liver is the largest internal organ in the body. It processes and stores nutrients and produces cholesterol and proteins such as albumin, clotting factors and the lipoproteins that carry cholesterol. It also secretes bile and performs many metabolic functions, including detoxification of several classes of *carcinogens*.

Classification. Most of the available data are on *hepatocellular carcinoma*, the best characterised and most common form of liver cancer. However, different outcomes are reported for unspecified primary liver cancer than for hepatocellular carcinoma and *cholangiocarcinoma*, so the different types of liver cancer may be a cause of heterogeneity among the study results.

Other established causes. Other established causes of liver cancer include the following:

Disease

Cirrhosis of the liver increases the risk of liver cancer [37].

Medication

Long-term use of oral contraceptives containing high doses of *oestrogen* and *progesterone* increases the risk of liver cancer [38].

Infection

Chronic infection with the hepatitis B or C virus is a cause of liver cancer [39].

Smoking tobacco

Smoking tobacco increases the risk of liver cancer generally, but there is a further increase in risk among people who smoke and have the hepatitis B or hepatitis C virus infection and also among people who smoke and consume large amounts of alcohol [7, 40]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [11].

Confounding. Smoking tobacco and hepatitis B and C viruses are possible *confounders* or *effect modifiers*.

For more detailed information on *adjustments* made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.3**).

The Panel is aware that alcohol is a cause of *cirrhosis*, which predisposes to liver cancer. Studies identified as focusing exclusively on patients with hepatic cirrhosis (including only patients with cirrhosis), hepatitis B or C viruses, alcoholism or history of alcohol abuse were not included in the CUP.

4.2.2.7 Colorectum

Definition. The *colon* (large intestine) is the lower part of the intestinal tract, which extends from the *caecum* (an intraperitoneal pouch) to the *rectum* (the final portion of the large intestine which connects to the anus).

Classification. Approximately 95 per cent of colorectal cancers are *adenocarcinomas*. Other types of colorectal cancers include *mucinous carcinomas* and *adenosquamous carcinomas*. *Carcinogens* can interact directly with the cells that line the colon and rectum.

Other established causes. Other established causes of colorectal cancer include the following:

Other diseases

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of, and so may be seen as a cause of, colon cancer [41].

Smoking tobacco

There is an increased risk of colorectal cancer in people who smoke tobacco. It has been estimated that 12 per cent of cases of colorectal cancer are attributable to smoking cigarettes [42].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [43]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [44]. The two major ones are *familial* adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.

Confounding. Smoking tobacco is a possible *confounder*. In postmenopausal women, *menopausal hormone therapy* (MHT) use decreases the risk of colorectal cancer and is a potential confounder.

For more detailed information on *adjustments* made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.4**).

4.2.2.8 Breast

Definition. Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts and connective tissue. Breast tissue develops in response to *hormones* such as *oestrogens*, *progesterone*, insulin and growth factors. The main periods of development are during puberty, pregnancy and lactation. The glandular tissue atrophies after *menopause*.

Classification. Breast cancers are almost all *carcinomas* of the *epithelial* cells lining the breast ducts (the channels in the breast that carry milk to the nipple). Fifteen per cent of breast cancers are lobular carcinoma (from lobes); most of the rest are ductal carcinoma. Although breast cancer can occur in men, it is rare (less than one per cent of cases) and thus is not included in the CUP.

Breast cancers are classified by their receptor type; that is, to what extent the cancer cells have receptors for the sex *hormones* oestrogen and progesterone, and the growth factor human epidermal growth factor (hEGF), which can affect the growth of the breast cancer cells. Breast cancer cells that have oestrogen receptors are referred to as oestrogen-receptor-positive (ER-positive), while those containing progesterone receptors are called progesterone-receptor-positive (PR-positive) cancers, and those with receptors for hEGF are HER2-receptor-positive (HER2-positive). Hormone-receptor-positive cancers are the most common subtypes of breast cancer but vary by population (60 to 90 per cent of cases). They have a relatively better prognosis than hormone-receptor-negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat.

Most data come from *high-income* countries. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods. Due to the importance of menopausal status as an *effect modifier*, studies should stratify for *menopause* status, but many do not.

Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to hormone receptor status or molecular intrinsic markers. Although there is growing evidence that these subtypes have different causes, most studies have limited statistical power to evaluate effects by subtype.

There is growing evidence that the impact of *obesity* and dietary exposures on the risk of breast cancer may differ according to these particular molecular subtypes of cancer, but currently there is no information on how nutritional factors might interact with these characteristics.

Other established causes. Other established causes of breast cancer include the following:

Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to *oestrogen* and progesterone and the risk of breast cancer [45–47]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [45, 46].

Because nutritional factors such as obesity can influence these life course processes, their impacts on breast cancer risk may depend on the maturational stage at which the exposure occurs. For instance, obesity before menopause is associated with reduced breast cancer risk, probably due to reduced ovarian progesterone production, while in postmenopausal women, in whom ovarian oestrogen production is low, obesity increases breast cancer risk by increasing production of oestradiol through the action of aromatase in adipose tissue.

Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [48, 49].

Medication

MHT (containing oestrogen or progesterone) increases the risk of breast cancer [50]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [51].

Family history

Some inherited mutations, particularly in *BRCA1, BRCA2* and *p53*, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [52].

Confounding. Use of MHT is an important possible *confounder* or *effect modifier* in postmenopausal breast cancer. High-quality studies adjust for age, number of reproductive cycles, age at which children were born and the use of hormone-based medications.

For more detailed information on *adjustments* made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Sections 5.1.5** and **5.1.7**).

4.2.2.9 Kidney

Definition. The kidneys are a pair of organs located at the back of the abdomen outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureters.

Classification. Different subtypes of kidney cancer likely have different aetiologies, yet some epidemiologic studies do not distinguish the *clear cell subtype*, the predominant parenchymal renal cancer, from *papillary* or other subtypes. Cancers of the renal pelvis are typically *transitional cell carcinomas*, which probably share aetiologic risk factors such as smoking tobacco with other transitional cell carcinomas of the ureter and bladder.

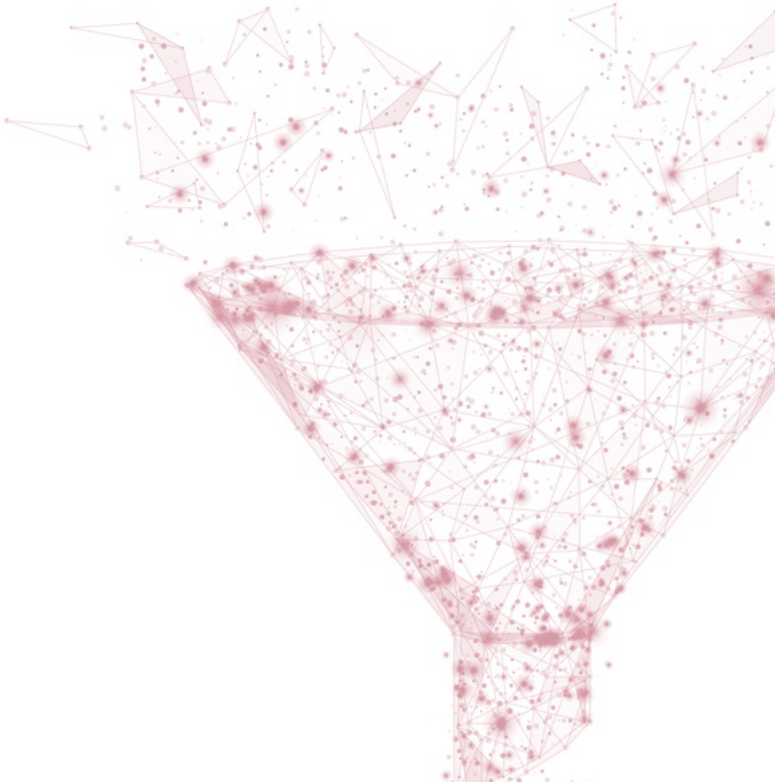
Other established causes. Other established causes of kidney cancer include the following:

Smoking tobacco

Smoking tobacco is a cause of kidney cancer. People who smoke have a 52 per cent increased risk of kidney cancer, and people who used to smoke have a 25 per cent increased risk, compared with those who have never smoked [53].

Medication

Painkillers containing phenacetin are known to cause cancer of the renal pelvis. Phenacetin is no longer used as an ingredient in painkillers [54].



Kidney disease

Polycystic kidney disease predisposes people to developing kidney cancer [55].

Hypertension

High blood pressure is associated with a higher risk of kidney cancer [56].

Family history

Inherited genetic predisposition accounts for only a minority of kidney cancers [57]. Von Hippel-Lindau syndrome is the most common, with up to 40 per cent of those inheriting the mutated gene developing kidney cancer [58].

Confounding. Smoking tobacco is a possible *confounder*.

For more detailed information on *adjustments* made in CUP analyses on alcoholic drinks, see Evidence and judgements (**Section 5.1.8**).

4.2.2.10 Skin

Definition. The skin is the outer covering of the body and is one of the largest organs in terms of surface area and weight. Its primary function is to act as a barrier between the body and the environment.

Classification. There are two main types of skin cancer: *melanoma* and *non-melanoma*. The most common non-melanoma tumours are *basal cell carcinoma* and *squamous cell carcinoma*, which together account for 90 per cent of skin cancers. Melanoma accounts for four per cent of skin cancers.

Other established causes. Other established causes of skin cancer include the following:

Radiation

Over-exposure to ultraviolet radiation (mainly from sunlight, but also from ultraviolet-emitting tanning devices) is the chief cause of melanoma and non-melanoma skin cancers [59, 60].

Medication

Immune suppression following organ transplantation is associated with an increased risk of skin cancers, especially *squamous cell carcinoma* [61].

Infection and infestation

HPV can cause *squamous cell carcinomas* of the skin, especially in immunocompromised people [61]. Patients with AIDS, who are immunocompromised, are also at increased risk of squamous cell carcinoma, but development of Kaposi's sarcoma, which is otherwise rare, is a characteristic complication.

Occupational exposure

Exposure to polychlorinated biphenyls (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for this cancer.

Family history and ethnicity

People who have a family history of *melanoma* may be predisposed to this type of skin cancer [62]. Non-melanoma and melanoma skin cancer is more common in lighter-skinned populations than in darker-skinned populations due to their paler skin pigmentation [59].

Confounding. Sun exposure is an important *confounder*.

5. Evidence and judgements

For information on study types, methods of assessment of exposures and methods of analysis used in the CUP, see Judging the evidence.

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,[1] there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. This section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on alcoholic drinks and the risk of cancer.

Note that, throughout this section, if *Egger's test*, *non-linear analysis* or stratified analyses are not mentioned for a particular exposure and cancer, it can be assumed that no such analyses were conducted. This is often because there were too few studies with the required information.

5.1 Alcoholic drinks

Table 5.1 summarises the main findings from the CUP *dose–response meta-analyses* of *cohort studies* on alcohol (as ethanol) and the risk of cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion:[2] nasopharynx (2017), oesophagus (adenocarcinoma; 2016), gallbladder (2015), ovary (2014), endometrium (2013), cervix (2017), prostate (2014), bladder (2015) and skin (squamous cell carcinoma, 2017).

The strong evidence on the effects of drinking alcohol on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses and information on mechanisms that could plausibly influence the risk of cancer.

For more information on the evidence for drinking alcohol and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP documents:

- CUP lung cancer report 2017: Section 7.12 and CUP lung cancer SLR 2015: Section 5.4.
- CUP pancreatic cancer report 2012: Section 7.5 and CUP pancreatic cancer SLR 2011: Section 3.7.1.
- CUP skin cancer SLR 2017: Section 3.7.1.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**.

Please note that the information on mechanisms included in the following subsections and in the appendix supersedes that in CUP cancer reports published before this Third Expert Report.

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin. CUP cancer reports not are currently available for nasopharynx, cervix and skin.

[2] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

Table 5.1: Summary of CUP dose–response meta-analyses for the risk of cancer, per 10 grams increase in alcohol (as ethanol)[1] consumed per day

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	I^2 (%)	Conclusion[2]	Date of CUP cancer report[3]
Mouth, pharynx and larynx (oral cavity cancer)	12	6	5,617	1.15 (1.09–1.22)	88	Convincing: Increases risk	2018
Mouth, pharynx and larynx (pharyngeal cancer)	8	4	342	1.13 (1.05–1.21)	61		
Mouth, pharynx and larynx (oral cavity and pharyngeal cancer combined)	10	5	954	1.19 (1.10–1.30)	83		
Mouth, pharynx and larynx (laryngeal cancer)	13	6	781	1.09 (1.05–1.13)	33		
Mouth, pharynx and larynx (head and neck cancer)[4]	3	–	–	Significant increased risk in 3 studies	–		
Mouth, pharynx and larynx (upper aerodigestive tract cancer)	10	9	1,826	1.18 (1.10–1.26)	95		
Oesophagus *(squamous cell carcinoma)*	8	6	1,079	1.25 (1.12–1.41)	95	Convincing: Increases risk	2016
Liver[5]	19	14	5,650	1.04 (1.02–1.06)	64	Convincing: Increases risk	2015
Colorectum[6]	19	16	15,896	1.07 (1.05–1.08)	28	Convincing: Increases risk	2017
Breast (postmenopause)[7]	34	22	35,221	1.09 (1.07–1.12)	71	Convincing: Increases risk	2017
Stomach[5]	30	23	11,926	1.02 (1.00–1.04)	39	Probable: Increases risk	2016
Breast (premenopause)[7]	16	10	4,227	1.05 (1.02–1.08)	0	Probable: Increases risk	2017
Lung	45	26	21,940	1.03 (1.01–1.05)	67	Limited – suggestive: Increases risk	2017
Pancreas[5]	10	9	3,096	1.00 (0.99–1.01)	0	Limited – suggestive: Increases risk	2012
Skin (malignant *melanoma*)	7	6	7,367	1.08 (1.03–1.13)	66	Limited – suggestive: Increases risk	2017
Skin (*basal cell carcinoma*)	9	9	3,349	1.04 (0.99–1.10)	68	Limited – suggestive: Increases risk	2017
Kidney[8]	8	7	3,525	0.92 (0.86–0.97)	55	Probable: Decreases risk	2015

Please see next page for explanation of footnotes.

1 Alcoholic drinks include beers, wines, spirits, fermented milks, mead and cider. The consumption of alcoholic drinks is graded by the International Agency for Research on Cancer as carcinogenic to humans (Group 1) [3].

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Alcoholic drinks and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing', 'probable' and 'limited – suggestive'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. All three studies (two highest versus lowest meta-analyses and one dose–response meta-analysis) identified on alcoholic drinks and head and neck cancers reported a statistically significant increased risk.

5 The conclusions for alcoholic drinks and cancers of the liver, stomach and pancreas were based on evidence for alcohol intakes above approximately 45 grams of ethanol per day (about three drinks a day). No conclusions were possible for these cancers based on intakes below 45 grams of ethanol per day.

6 The conclusion for alcoholic drinks and colorectal cancer was based on alcohol intakes above approximately 30 grams of ethanol per day (about two drinks a day). No conclusion was possible based on intakes below 30 grams of ethanol per day.

7 No threshold level of alcohol intake was identified in the evidence for alcoholic drinks and breast cancer (pre and postmenopause).

8 The conclusion for alcoholic drinks and kidney cancer was based on alcohol intakes up to approximately 30 grams of ethanol per day (about two drinks a day). There was insufficient evidence to draw a conclusion for intakes above 30 grams of ethanol per day.

5.1.1 Mouth, pharynx and larynx

(Also see CUP mouth, pharynx and larynx cancer report 2018: Section 7.5 and CUP mouth, pharynx and larynx cancer SLR 2016: Section 3.7.)

The evidence for oral cavity cancer, oral cavity and pharyngeal cancer combined, pharyngeal cancer, laryngeal cancer, head and neck cancer, and upper aerodigestive tract cancer is presented in the following subsections. Dose–response meta-analyses in this section include studies reporting on incidence and/or mortality.

5.1.1.1 Oral cavity cancer

CUP dose–response meta-analyses

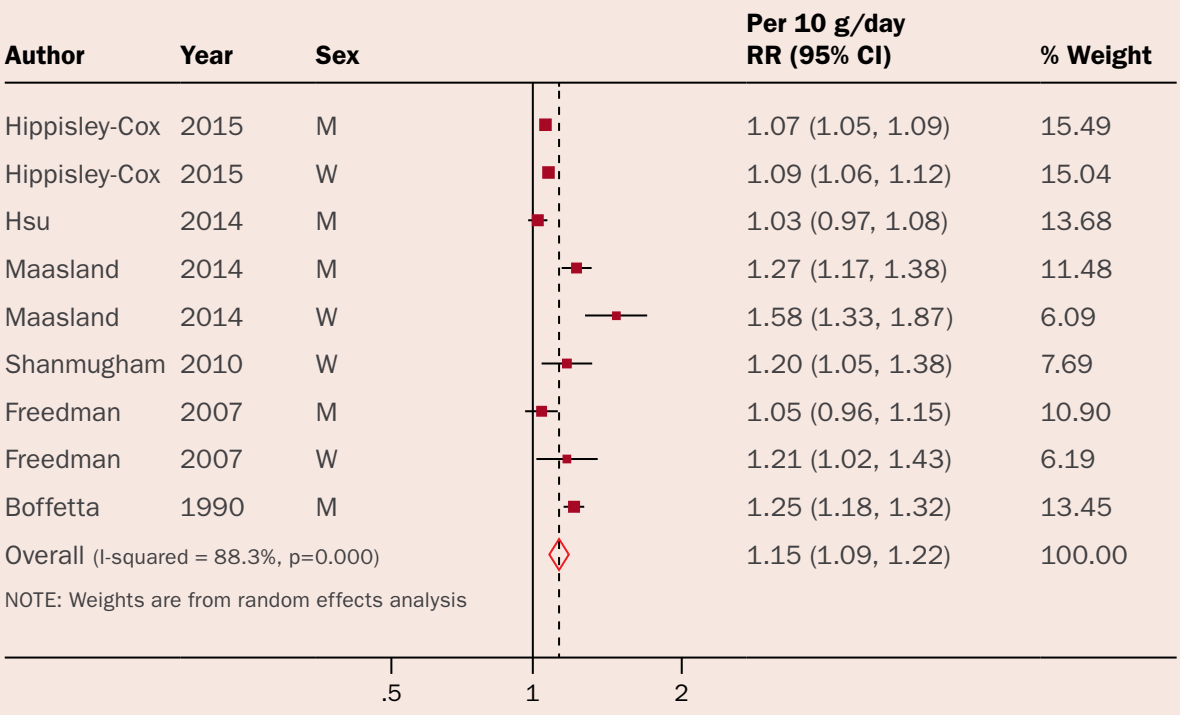
Six of 12 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 15 per cent increased risk of oral cavity cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.15 [95% CI 1.09–1.22]; n = 5,617) (see **Figure 5.1**). High *heterogeneity* was observed (I^2 = 88%).

There was evidence of small study bias with *Egger's test* (p = 0.04; see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 10). Inspection of the funnel plot identified three studies as outliers [8, 63, 64].

A stratified analysis of the risk of oral cavity cancer per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for sex; a statistically significant increased risk was observed for both men (RR 1.13 [95% CI 1.04–1.22]) and women (RR 1.24 [95% CI 1.07–1.45]) although high *heterogeneity* persisted (see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 9).

Interactions with smoking or chewing tobacco were investigated in four published studies; two studies were included in the CUP dose–response meta-analysis [8, 66] and two studies were not [68, 69]. An increase in the risk of oral cavity cancer was observed for the highest compared with the lowest intake of alcohol (as ethanol) in people who smoked, although not all studies reported statistically significant results. In one published study [8], a significant increased risk was observed in people who have never smoked (RR 4.16 [95% CI 1.82–9.52]) as well as in those who have smoked (RR 3.54 [95% CI 1.66–7.52]).

Figure 5.1: CUP dose–response meta-analysis[1,2] for the risk of oral cavity cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Hippisley-Cox, 2015 [65]; Hsu, 2014 [63]; Maasland, 2014 [8]; Shanmugham, 2010 [66]; Freedman, 2007 [67]; Boffetta, 1990 [64].

All studies included in the dose–response meta-analysis adjusted for tobacco smoking. For information on the *adjustments* made in individual studies, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 8.

Published pooled analyses and meta-analyses

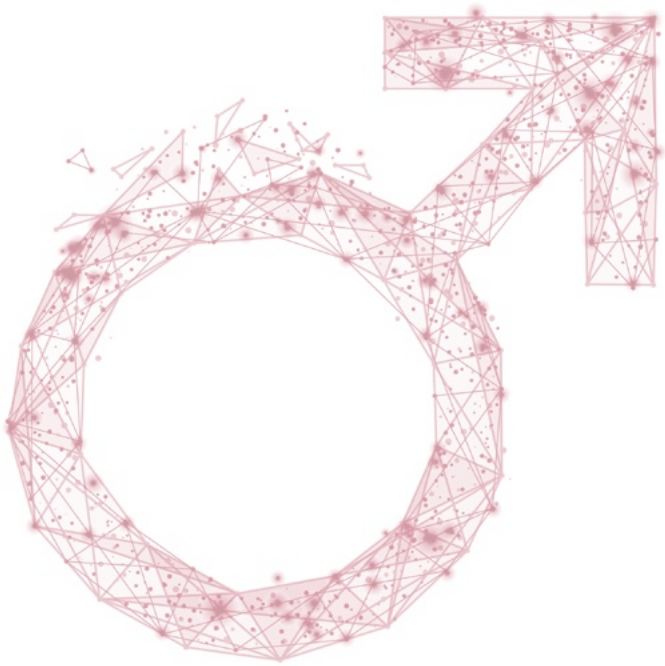
One published *pooled analysis* (see **Table 5.2**) on consumption of alcohol and the risk of oral cavity cancer was identified. No other published meta-analyses have been identified. The pooled analysis of 15 *case-control studies* [70] reported an increased risk for consumption of five to 10 alcoholic drinks per day compared with less than one alcoholic drink per day which was statistically significant for men, but not women.

Table 5.2: Summary of published pooled analyses of alcohol intake and the risk of oral cavity cancer

Publication	Contrast	Sex	RR (95% CI)	P trend	No. studies (case-control)	No. cases
Lubin, 2011 [70]	5 to 10 drinks/day vs 0.01 to 0.9 drinks/day	Men	1.75 (1.1–2.8)	< 0.01	15	1,333
		Women	2.37 (0.8–7.5)	< 0.01		456

[1] Six studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 9.
[2] A total of six studies was analysed in the CUP dose–response meta-analysis. In some studies, the relative risk for men and women was reported separately.

5.1.1.2 Pharyngeal cancer

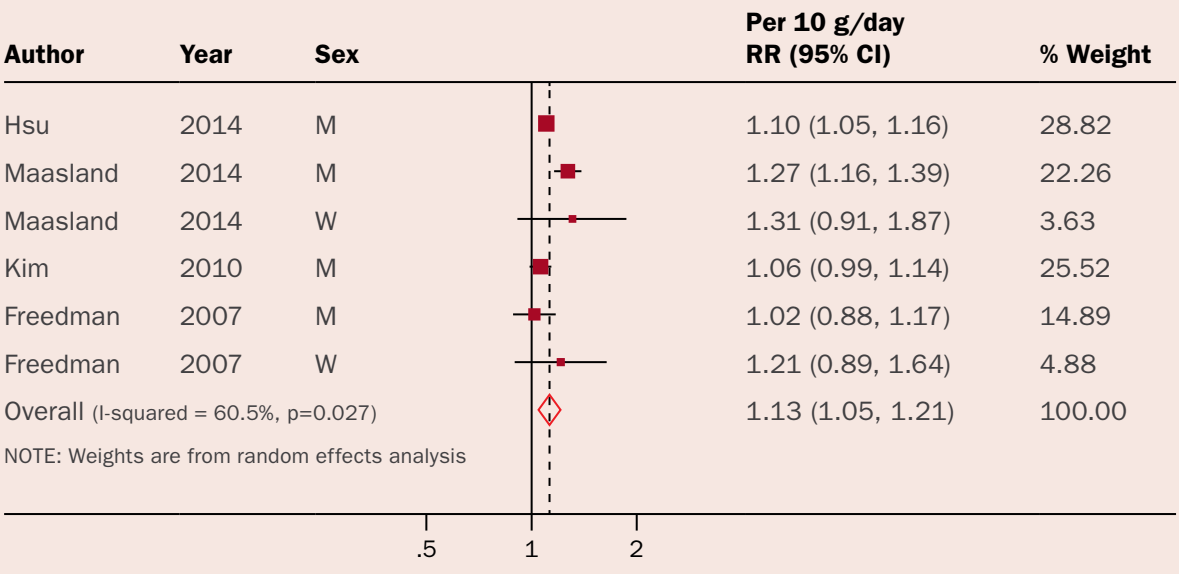


CUP dose–response meta-analyses

Four of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant 13 per cent increased risk of pharyngeal cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.13 [95% CI 1.05–1.21]; n = 342) (see **Figure 5.2**). High *heterogeneity* was observed (I^2 = 61%).

A stratified analysis of the risk of pharyngeal cancer per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for sex; a statistically significant increased risk was observed for men (RR 1.11 [95% CI 1.03–1.21]), but not women (RR 1.25 [95% CI 0.99–1.58]); see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 18).

Figure 5.2: CUP dose–response meta-analysis[1,2] for the risk of pharyngeal cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Hsu, 2014 [63]; Maasland, 2014 [8]; Kim, 2010 [71]; Freedman, 2007 [67].

[1] Four studies could not be included in the dose–response meta-analysis, because sufficient information was not provided. For further details, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 15.

[2] A total of four studies was analysed in the CUP dose–response meta-analysis. In some studies, the relative risk for men and women was reported separately.

Several published studies stratified by tobacco smoking and alcohol consumption. One published study included in the dose–response meta-analysis [8] reported a significant increased risk for people who drank more than 15 grams of alcohol (as ethanol) per day and smoked (≥ 20 cigarettes per day) compared with people who drank less alcohol (0 to 15 grams of alcohol [as ethanol] per day) and had never smoked (RR 16.12 [95% CI 4.31–60.71], n = 31 cases). A significant increased risk was also observed for people who drank more than 15 grams of alcohol (as ethanol) per day and who had never smoked compared with people who drank less alcohol (0 to 15 grams [as ethanol] per day) and had never smoked (RR 10.18 [95% CI 2.03–51.06], n = 3 cases). No significant interaction was found between categories of alcohol consumption and tobacco smoking (p = 0.09). Another published cohort study not included in the dose–response meta-analysis [72] reported no significant association between drinking alcohol and chewing tobacco.

All studies included in the dose–response meta-analysis adjusted for tobacco smoking. For information on the adjustments made in individual studies, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 15.

Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.3**) on consumption of alcohol and the risk of pharyngeal cancer was identified. No other published meta-analyses have been identified. The pooled analysis of 15 *case-control studies* [70], reported a statistically significant increased risk in both men and women separately for five to 10 alcoholic drinks per day compared with less than one drink per day for both oropharyngeal and hypopharyngeal cancers.

5.1.1.3 Oral cavity and pharyngeal cancer combined

CUP dose–response meta-analyses

Five of 10 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 19 per cent increased risk of oral cavity and pharyngeal cancer combined per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.19 [95% CI 1.10–1.30]; n = 954) (see **Figure 5.3**). High *heterogeneity* was observed (I^2 = 83%) mainly explained by a large increased risk reported in one study [73].

Table 5.3: Summary of published pooled analyses of alcohol (as ethanol) intake and the risk of pharyngeal cancer

Publication	Contrast	Cancer	Sex	RR (95% CI)	P trend	No. studies (case-control)	No. cases
Lubin, 2011 [70]	5 to 10 drinks/day vs 0.01 to 0.9 drinks/day	Oropharyngeal	Men	2.82 (1.8–4.3)	< 0.01	15	1,528
			Women	7.63 (2.8–21.0)	< 0.01		404
		Hypopharyngeal	Men	7.03 (2.6–19.0)	< 0.01		395
			Women	19.60 (1.8–217.0)	< 0.01		77

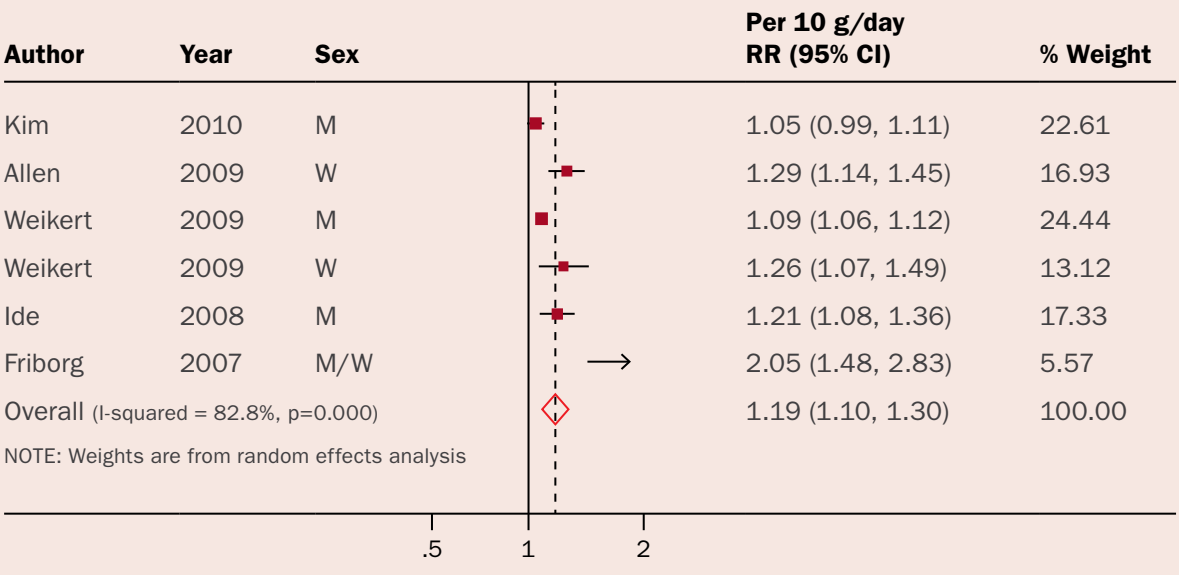
There was evidence of small study bias with *Egger's test* (p = 0.04). Inspection of the funnel plot showed asymmetry, with two studies [73, 74] reporting a larger increased risk than expected (see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 15).

A stratified analysis of the risk of oral cavity and pharyngeal cancer combined per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for sex; a statistically significant increased risk was observed for both men (RR 1.09 [95% CI 1.04–1.15]) and women (RR 1.28 [95% CI 1.16–1.41]; see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 14).

Two studies that were included in the dose–response meta-analysis for alcohol (as ethanol) and the risk of oral cavity and pharyngeal cancer stratified by tobacco smoking status and alcohol consumption. In one study of cancer mortality in men [76], a significant increased risk was observed for men who smoke and drink alcohol compared with men who never smoked and never drank alcohol (RR 3.3 [95% CI 1.1–9.6]). In men who never smoked, consuming alcohol did not alter the risk of oral cavity and pharyngeal cancer [76]. In another study [73], a significant increased risk was observed in people who drank more than seven alcoholic drinks per week if they had smoked for fewer than 39 years (RR 4.9 [95% CI 1.3–18.5]) or more than 39 years (RR 18.4 [95% CI 7.5–14.5]) compared with people who did not smoke or consume alcohol.

All studies included in the dose–response meta-analysis adjusted for tobacco smoking. For information on the adjustments made in individual studies, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 12.

Figure 5.3: CUP dose–response meta-analysis[1,2] for the risk of oral cavity and pharyngeal cancer combined, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Kim, 2010 [71]; Allen, 2009 [74]; Weikert, 2009 [75]; Ide, 2008 [76]; Friborg, 2007 [73].

[1] Five studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 13.
[2] A total of five studies was analysed in the CUP dose–response meta-analysis. In one study, the relative risk for men and women was reported separately.

Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on alcohol intake and the risk of oral and pharyngeal cancer combined has been identified. In the meta-analysis of five cohorts [77], a statistically significant increased risk was observed in people who drank a moderate level of alcohol (≤ 50 grams of ethanol per day; RR 1.25 [95% CI 1.02–1.53]) and a high level of alcohol (> 50 grams of ethanol per day; RR 3.13 [95% CI 1.59–6.19]) compared with people who do not regularly drink alcohol.

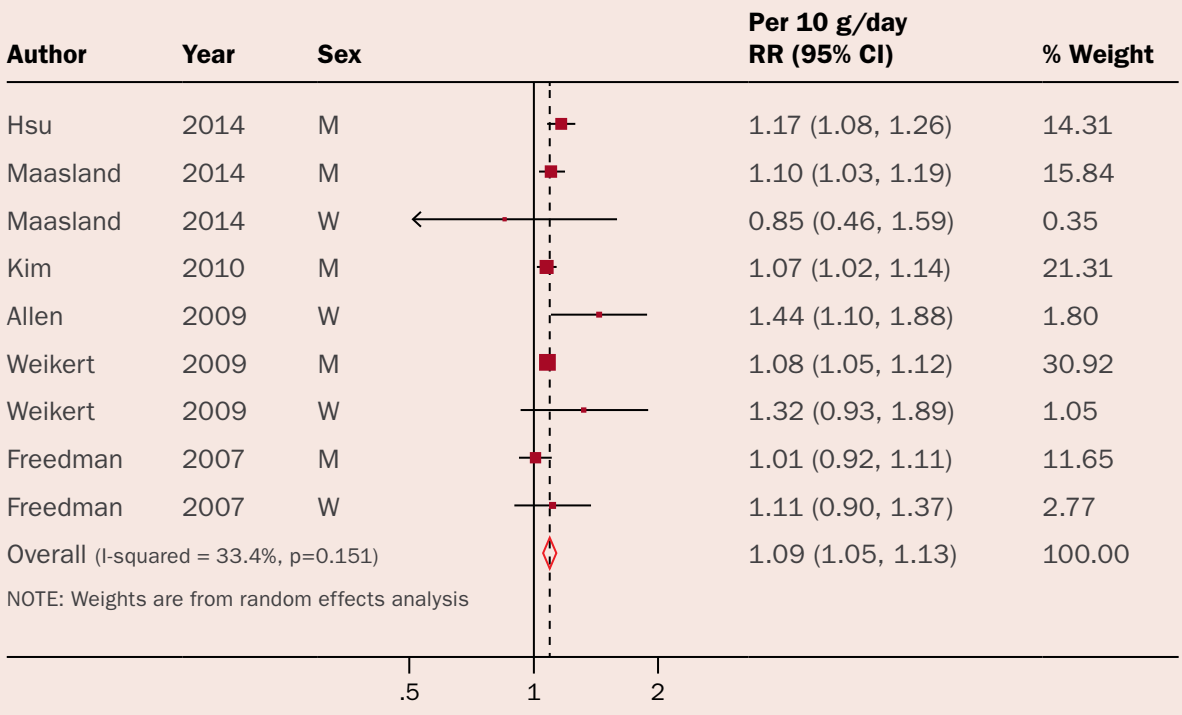
5.1.1.4 Laryngeal cancer

CUP dose–response meta-analyses

Six of 13 identified studies were included in the dose–response meta-analysis, which showed a statistically significant nine per cent increased risk of laryngeal cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.09 [95% CI 1.05–1.13]; n = 781) (see **Figure 5.4**). Moderate *heterogeneity* was observed (I^2 = 33%).

There was no evidence of small study bias with *Egger's test* (p = 0.37); however, the study of women by Allen and colleagues. (2009) was an outlier [74].

Figure 5.4: CUP dose–response meta-analysis[1,2] for the risk of laryngeal cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Hsu, 2014 [63]; Maasland, 2014 [8]; Kim, 2010 [71]; Allen, 2009 [74]; Weikert, 2009 [75]; Freedman, 2007 [67].

[1] Seven studies could not be included in the dose–response meta-analysis, because sufficient information was not provided. For further details, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 19.

[2] A total of four studies was analysed in the CUP dose–response meta-analysis. In some studies, the relative risk for men and women was reported separately.

A stratified analysis of the risk of laryngeal cancer per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for sex; a statistically significant increased risk was observed for both men (RR 1.09 [95% CI 1.05–1.12]) and women (RR 1.22 [95% CI 1.03–1.45]; see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 22).

Several published studies not included in the CUP dose–response meta-analysis have shown that people who had alcoholism had a significantly increased risk of laryngeal cancer compared with those who did not [78–80].

One published study that was included in the dose–response meta-analysis [8] reported a significant increased risk of laryngeal cancer for people who drank more than 15 grams of alcohol (as ethanol) per day and who smoked (≥ 20 cigarettes per day) compared with people who drank less alcohol (0 to 15 grams of alcohol [as ethanol] per day) and had never smoked (RR 5.54 [95% CI 2.15–14.27]). No significant interaction was found between categories of alcohol consumption and cigarette smoking (p = 0.19).

All studies included in the dose–response meta-analysis adjusted for tobacco smoking. For information on the *adjustments* made in individual studies, see CUP mouth, pharynx and larynx cancer SLR 2016, Table 18.

Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.4**) and one other published meta-analysis on consumption of alcohol and the risk of laryngeal cancer were identified. The pooled analysis of 15 *case-control studies* reported a statistically significant increased risk in men for consuming five to 10 alcoholic drinks per day compared with less than one alcoholic drink per day, but not in women [70]. The meta-analysis of three cohort studies reported no significant association in people who drank a low, moderate or high level of alcohol compared with people who do not regularly drink alcohol [77].

5.1.1.5 Head and neck cancer

Published cohort studies

No highest versus lowest or dose–response meta-analyses were conducted in the CUP. However, three published cohort studies were identified on total alcohol consumption and the risk of head and neck cancer; a significant increased risk was observed in all three studies [8, 81, 82]. Two studies compared the highest with the lowest level of alcohol intake, and one study conducted a dose–response meta-analysis. Three identified studies adjusted for smoking tobacco (see **Table 5.5**).

Table 5.4: Summary of published pooled analyses of alcohol intake and the risk of laryngeal cancer

Publication	Contrast	Sex	RR (95% CI)	P trend	No. studies (case-control)	No. cases
Lubin, 2011 [70]	5 to 10 drinks/ day vs 0.01 to 0.9 drinks/day	Men	1.89 (1.10–3.10)	< 0.01	15	1,361
		Women	0.52 (0.10–2.70)	0.88		

Table 5.5: Summary of published cohort studies of alcohol intake and the risk of head and neck cancer

Publication	Increment/contrast	Sex	RR (95% CI)	No. cases
Maasland, 2014 [8]	Per 10 g/day ethanol	Men	1.19 (1.12–1.27)	314
		Women	1.40 (1.18–1.65)	81
Hashibe, 2013 [82]	≥ 4 drinks/day vs none	Men and women	2.24 (1.37–3.65)	177
Freedman, 2007 [81]	> 3 drinks/day vs < 1 drink/day	Men	1.48 (1.15–1.90)	611
		Women	2.52 (1.46–4.35)	183

Two published studies stratified by tobacco smoking and alcohol consumption. In one study [8], where 506 of 550 cases were in people who smoked, a statistically significant increased risk of head and neck cancer was observed in people who drank alcohol (≥ 30 grams of ethanol per day) and smoked (≥ 20 cigarettes per day) compared with those who did not drink alcohol and had never smoked (RR 8.28 [95% CI 3.98–17.22], n= 80 cases; p = 0.03 for interaction). In another study [82], where 139 of 175 cases were in people who smoked, a significant increased risk was observed in people who drank alcohol (≥ two drinks per day) and smoked (≥ 20 cigarettes per day; RR 11.07 [95% CI 5.07–24.14]) compared with those who did not drink alcohol and had never smoked. In people who did not smoke, no significant association was observed between drinking alcohol and the risk of head and neck cancer.

Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of alcohol and the risk of head and neck cancer were identified.

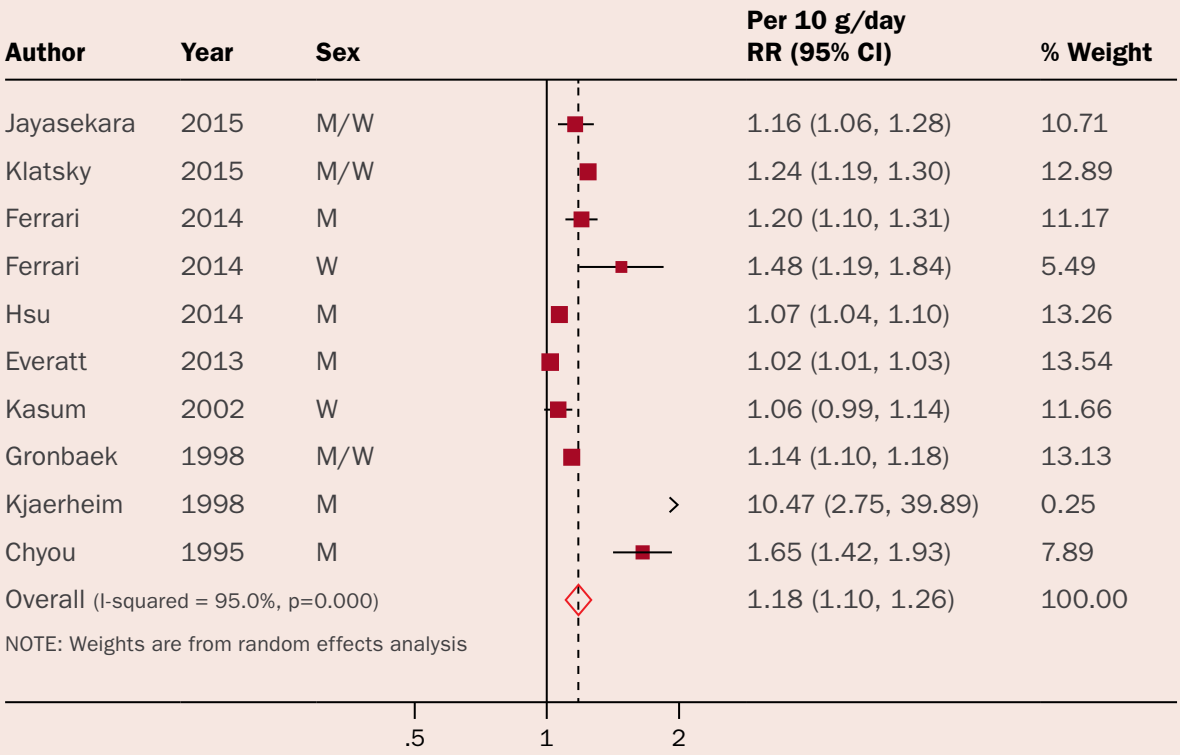
5.1.1.6 Upper aerodigestive tract cancer

CUP dose–response meta-analyses

Nine of 10 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 18 per cent increased risk of upper aerodigestive tract cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.18 [95% CI 1.10–1.26]; n = 1,826) (see **Figure 5.5**). High *heterogeneity* was observed (I^2 = 95%).

There was evidence of small study bias with Egger's test (p = 0.005). Inspection of the funnel plot showed asymmetry, with one small study [83] reporting a larger increase in risk than expected (see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 28).

Figure 5.5: CUP dose–response meta-analysis[1] for the risk of upper aerodigestive tract cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Jayasekara, 2015 [84]; Klatsky, 2015 [85]; Ferrari, 2014 [86]; Hsu, 2014 [63]; Everatt, 2013 [87]; Kasum, 2002 [88]; Gronbaek, 1998 [89]; Kjaerheim, 1998 [83]; Chyou, 1995 [90].

A stratified analysis of the risk of upper aerodigestive tract cancer per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for sex; a statistically significant increased risk was observed for both men (RR 1.17 [95% CI 1.08–1.27]) and women (RR 1.19 [95% CI 0.95–1.49]; see CUP mouth, pharynx and larynx cancer SLR 2016, Figure 27).

Three published studies that were included in the dose–response meta-analysis for intake of alcohol (as ethanol) and the risk of upper aerodigestive tract cancer looked at the interaction with smoking tobacco [63, 89, 90]. One study in Taiwan [63] reported a significant increased risk in men who chewed betel quid and smoked but never drank alcohol (RR 8.88 [95% CI 6.08–12.98]; n = 39 cases), and in men who chewed betel quid, smoked and drank alcohol (RR 12.04 [95% CI 7.66–18.93]; n = 33 cases), compared with men who never chewed betel quid, never smoked and never drank alcohol (n = 30 cases).

A study in Denmark [89] reported no significant interaction of alcohol and tobacco with the risk of upper aerodigestive tract cancers.

A study in Hawaiian men [90], reported a significant increased risk of upper aerodigestive tract cancer in men who drank more than 14 ounces (400 millilitres) of alcohol per week and who did not smoke compared with those who did not smoke or drink alcohol (RR 6.5 [95% CI 1.63–25.0]; n = 6 cases vs n = 3 cases). For the same comparison, a larger increased risk was observed in men who drank more than 14 ounces (400 millilitres) of

[1] A total of nine studies was analysed in the CUP dose–response meta-analysis. In one study, the relative risk for men and women was reported separately.

alcohol per week who also smoked more than 20 cigarettes per day (RR 14.35 [95% CI not reported], n = 28 cases).

All studies included in the dose–response meta-analysis adjusted for age and tobacco smoking. For information on the *adjustments* made in individual studies see CUP mouth, pharynx and larynx cancer SLR 2016, Table 23.

Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on consumption of alcohol and the risk of upper aerodigestive tract cancer has been identified. The meta-analysis of three cohort studies [91] showed a statistically significant increased risk when comparing the highest with the lowest level of alcohol consumed (RR 2.83 [95% CI 1.73–4.62]).

5.1.1.7 Other alcohol exposures

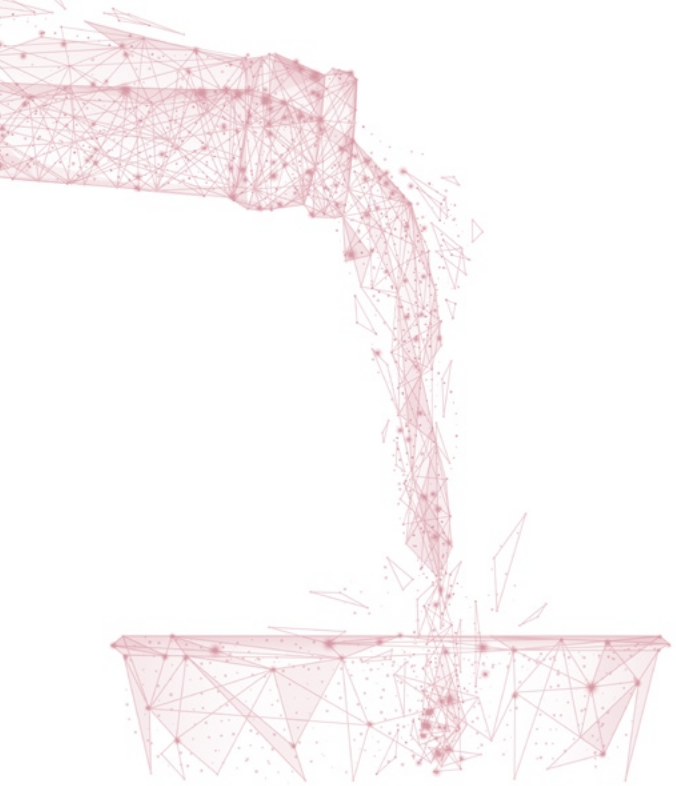
CUP dose–response meta-analyses

Separate dose–response meta-analyses were also conducted for the consumption of beer, wine and spirits and the risk of oral cavity cancer, pharyngeal cancer, laryngeal cancer, and head and neck cancer (see **Table 5.6** and CUP mouth, pharynx and larynx cancer SLR 2016, Figures 29, 30 and 31).

For both beer and spirits a statistically significant increased risk of head and neck cancer was observed. No significant association was observed between any of the cancers and drinking wine. All studies adjusted for smoking tobacco, but residual *confounding* due to different patterns of smoking among people who consume different types of alcoholic drink cannot be excluded.

Table 5.6: CUP dose–response meta-analyses for the risk of subtypes of cancer of the mouth, pharynx and larynx, per 10 grams increase in the specific type of alcohol consumed per day

Analysis	Cancer type	RR (95% CI)	I^2 (%)	No. studies
Beer	Oral cavity	1.14 (0.96–1.36)	74	2
	Pharyngeal	1.12 (1.02–1.24)	0	2
	Laryngeal	1.05 (0.98–1.13)	0	2
	Head and neck	1.09 (1.01–1.18)	49	2
Wine	Oral cavity	0.90 (0.77–1.06)	18	2
	Pharyngeal	0.99 (0.83–1.17)	0	2
	Laryngeal	0.93 (0.80–1.07)	0	3
	Head and neck	0.92 (0.83–1.02)	0	2
Spirits	Oral cavity	1.11 (1.02–1.21)	0	2
	Pharyngeal	1.08 (0.89–1.31)	55	2
	Laryngeal	1.04 (0.96–1.13)	0	2
	Head and neck	1.09 (1.02–1.15)	15	2



Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on consumption of beer, wine or spirits and the risk of cancers of the mouth, pharynx and larynx were identified.

5.1.1.8 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The precise mechanisms underlying the relationship between alcohol consumption and cancers of the mouth, pharynx and larynx are not completely understood. A large body of experimental evidence has shown that acetaldehyde, the major and most toxic metabolite of alcohol, disrupts DNA synthesis and repair and thus may contribute to a carcinogenic cascade [92, 93]. Higher ethanol consumption also induces oxidative stress through increased production of reactive oxygen species, which are potentially genotoxic [94]. It is hypothesised that alcohol may also function as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens* or interfere with DNA repair mechanisms [95]. High consumers of alcohol may also have diets that are lacking in essential nutrients, such as folate, rendering target tissues more susceptible to carcinogenic effects of alcohol.

5.1.1.9 CUP Panel's conclusion

The evidence was consistent, and dose–response meta-analyses showed a significant increased risk with increasing alcohol consumption. For oral cavity cancer, and oral cavity and pharyngeal cancer combined, a larger increase in risk was observed in women.

All studies included in the dose–response meta-analyses for alcohol (as ethanol) adjusted for tobacco smoking. Observations for smoking interactions were variable and the number of cases were limited, but several studies noted that the increased risk was attenuated in people who had never smoked.

The findings were generally consistent with one *pooled analysis* of *case-control studies* and two published meta-analyses of cohorts. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a convincing cause of cancers of the mouth, pharynx and larynx.**

5.1.2 Oesophagus (squamous cell carcinoma)

(Also see CUP oesophageal cancer report 2016: Section 7.5 and CUP oesophageal cancer SLR 2015: Sections 5.4.1, 5.4.2 and 5.4.3).

5.1.2.1 CUP dose–response meta-analyses

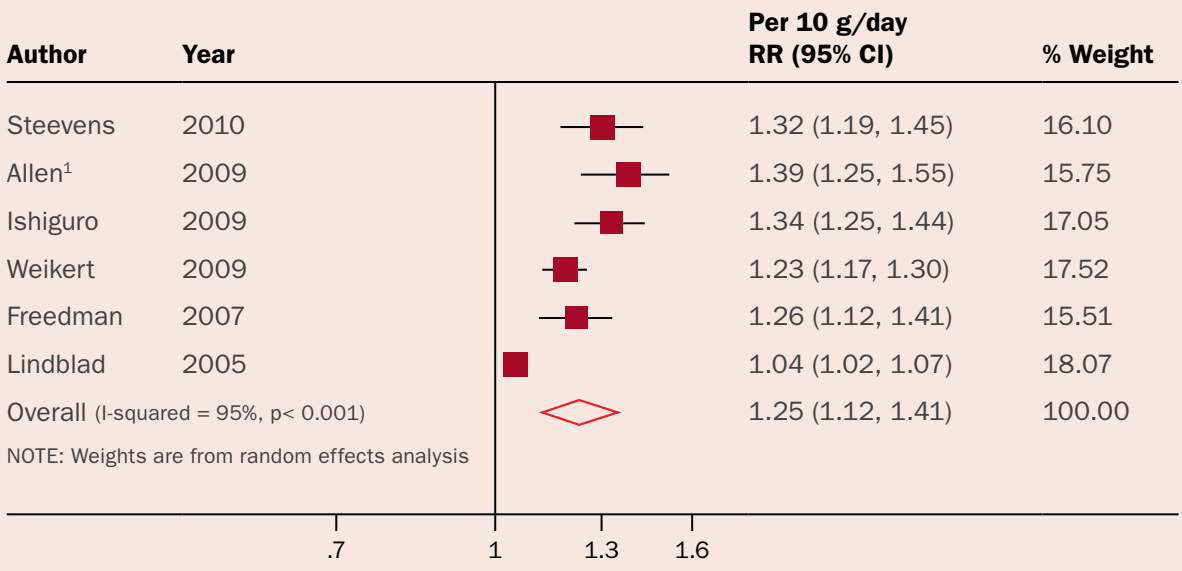
Six of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant 25 per cent increased risk of oesophageal cancer (*squamous cell carcinoma*) per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.25 [95% CI 1.12–1.41]; n = 1,079) (see **Figure 5.6**).

High *heterogeneity* was observed (I^2 = 95%). Inspection of the *forest plot* indicated that a substantial part of the heterogeneity was due to one study (Lindblad, 2005 [96]). After exclusion of this study, which analysed a computerised database of patient records rather than dietary intake questionnaires, the heterogeneity was lower (I^2 = 39%).

There was evidence of small study bias with *Egger's test* (p = 0.009). Inspection of the funnel plot identified the same study (Lindblad, 2005 [96]) as an outlier (see CUP oesophageal cancer SLR 2015, Figure 52). When this study was removed there was no evidence of small study bias (p = 0.29).

A stratified analysis for the risk of oesophageal cancer (squamous cell carcinoma) per 10 grams increase in alcohol (as ethanol) consumed per day was conducted for geographic location. Studies from Asia reported on oesophageal cancer (unspecified), and these were included as cancers in Asia are mostly squamous cell carcinomas. When stratified by geographic location, a statistically significant increased risk was observed for Asia (RR 1.34 [95% CI 1.19–1.51]), Europe (RR 1.23 [95% CI 1.07–1.42]) and North America (RR 1.26 [95% CI 1.12–1.41], single study; see CUP oesophageal cancer SLR 2015, Figure 55).

Figure 5.6: CUP dose–response meta-analysis for the risk of oesophageal cancer (squamous cell carcinoma),[1] per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Steevens, 2010 [97]; Allen, 2009 [74]; Ishiguro, 2009 [98]; Weikert, 2009 [75]; Freedman, 2007 [99]; Lindblad, 2005 [96].

[1] RR estimates of 'non-adenocarcinoma oesophageal cancers' were included in the analysis of oesophageal squamous cell carcinoma.

There was evidence of a non-linear dose–response relationship (p = 0.04; see **Figure 5.7** and **Table 5.7**), when analysing the studies reporting on oesophageal cancer (squamous cell carcinoma) and the studies on the incidence of oesophageal cancer (unspecified) in Asia. The Asian studies were included in this analysis as cancers in Asia are mostly squamous cell carcinomas. There was evidence of a steeper increase in risk for lower intakes; however, no threshold was detected. Most of the observations in the analysis were for intakes below 80 grams of alcohol (as ethanol) per day (see **Figure 5.7** and CUP oesophageal cancer SLR 2015, Table 43).

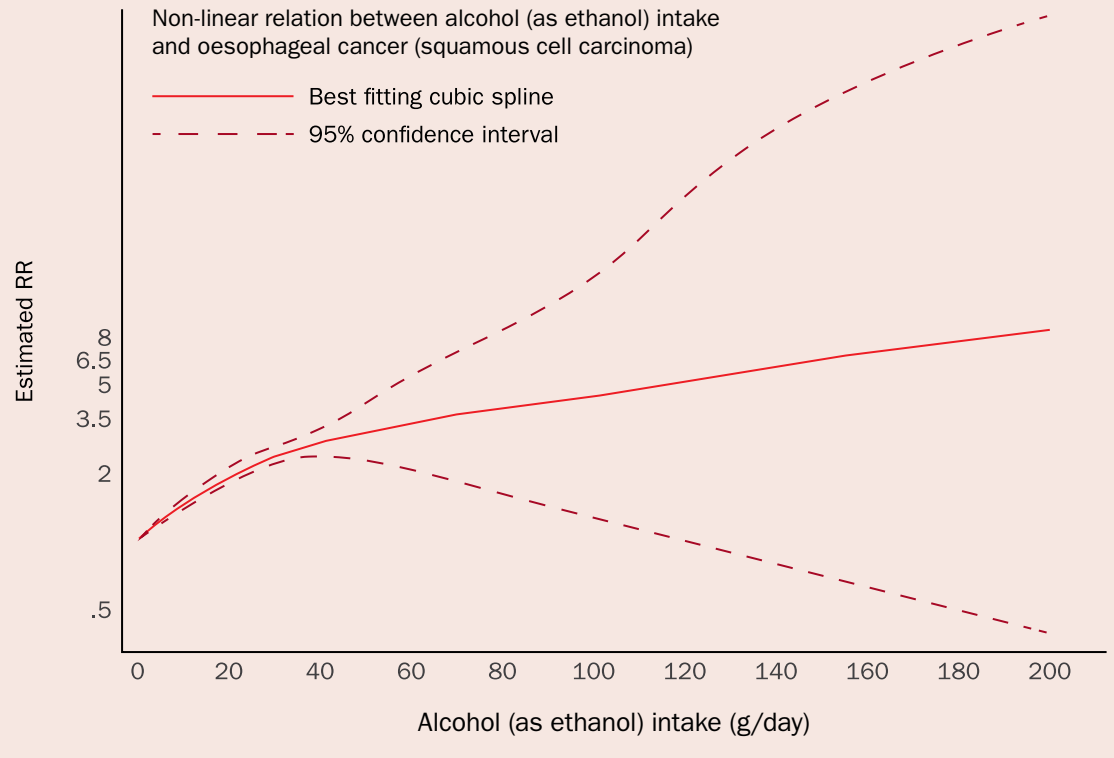
All studies included in the dose–response meta-analysis adjusted for age, sex and tobacco smoking. For information on the *adjustments* made in individual studies see CUP oesophageal cancer SLR 2015, Table 40.

Separate highest versus lowest meta-analyses conducted by type of alcoholic drink showed a significant increased risk for beer (RR 2.56 [95% CI 1.18–5.57]) and spirits (RR 3.41 [95% CI 2.16–5.38] including the studies in Asia) for the highest compared with the lowest level of alcohol consumed, but not for wine.

Table 5.7: CUP non-linear dose–response estimates of alcohol (as ethanol) intake and the risk of oesophageal cancer (squamous cell carcinoma), including the six studies shown in Figure 5.6 and studies from Asia on oesophageal cancer

Alcohol (as ethanol) intake (g/day)	RR (95% CI)
0	1.00
10	1.41 (1.31–1.52)
22	1.97 (1.79–2.17)
40	2.64 (2.24–3.11)
59.5	3.12 (1.90–5.12)
99.5	4.16 (1.17–14.77)

Figure 5.7: CUP non-linear dose–response association for alcohol (as ethanol) intake and the risk of oesophageal cancer (squamous cell carcinoma), including the six studies shown in Figure 5.6 and studies from Asia on oesophageal cancer



5.1.2.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.8**) and two other published meta-analyses on consumption of alcohol and the risk of oesophageal cancer (squamous cell carcinoma) were identified. The pooled analysis (of *cohort* and *case-control studies*) reported a statistically significant increased risk when comparing the highest with the lowest level of alcoholic drinks consumed [100].

Both meta-analyses of cohort studies reported an increased risk [101, 102], although only one was significant (RR 3.51 [95% CI 3.09–4.00] for more than 200 grams per week of alcohol [as ethanol] compared with never drinking alcohol) [102].

5.1.2.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Several mechanisms have been proposed to explain the association of alcohol drinking with oesophageal squamous cell carcinoma. Alcohol consumption can induce the expression of cytochrome P450 2E1 (CYP2E1) in the human oesophagus in a dose-dependent manner, and CYP2E1 activity yields substantial quantities of reactive oxygen species that may cause carcinogenic DNA lesions through oxidative stress inflammation, and lipid peroxidation [103]. Acetaldehyde, the major alcohol metabolite, may promote *carcinogenesis* by inhibiting DNA methylation or interacting with retinoid metabolism, both of which regulate the transcription of genes that have a key role in cellular growth and differentiation [92]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism, or interfere with retinoid metabolism and with DNA repair mechanisms [95].

5.1.2.4 CUP Panel's conclusion

For oesophageal cancer (squamous cell carcinoma), the evidence was consistent.

Table 5.8: Summary of published pooled analyses of alcohol intake and the risk of oesophageal cancer (squamous cell carcinoma)

Publication	Contrast	RR (95% CI)	p trend	No. studies	No. cases
BEACON Consortium [100]	≥ 7 drinks/day vs none	9.62 (4.26–21.71)	< 0.0001	5 case-control, 2 cohort	1,016

The dose–response meta-analysis showed a statistically significant increased risk with higher alcohol consumption. There was evidence of high *heterogeneity*, but this appeared to be due to the size of the effect. There was a suggestion of non-linearity, with a steeper increase in risk for lower intakes of alcohol. No threshold was detected. All studies adjusted for tobacco smoking.

The findings of the CUP analyses were consistent with one *pooled analysis* and two published meta-analyses. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a convincing cause of oesophageal squamous cell carcinoma.**

5.1.3 Liver

(Also see CUP liver cancer report 2015: Section 7.4 and CUP liver cancer SLR 2014: Section 5.4).

5.1.3.1 CUP dose–response meta-analyses

Fourteen of 19 identified studies were included in the dose–response meta-analysis, which showed a statistically significant four per cent increased risk of liver cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.04 [95% CI 1.02–1.06]; n = 5,650) (see **Figure 5.8**).

High *heterogeneity* was observed (I^2 = 64%), which appeared to be mainly due to the size of the effect. There was evidence of small study bias with *Egger's test* (p = 0.001). Inspection of the funnel plot showed that small studies with risk estimates of less than 1.04 may be missing (see CUP liver cancer SLR 2014, Figure 39).

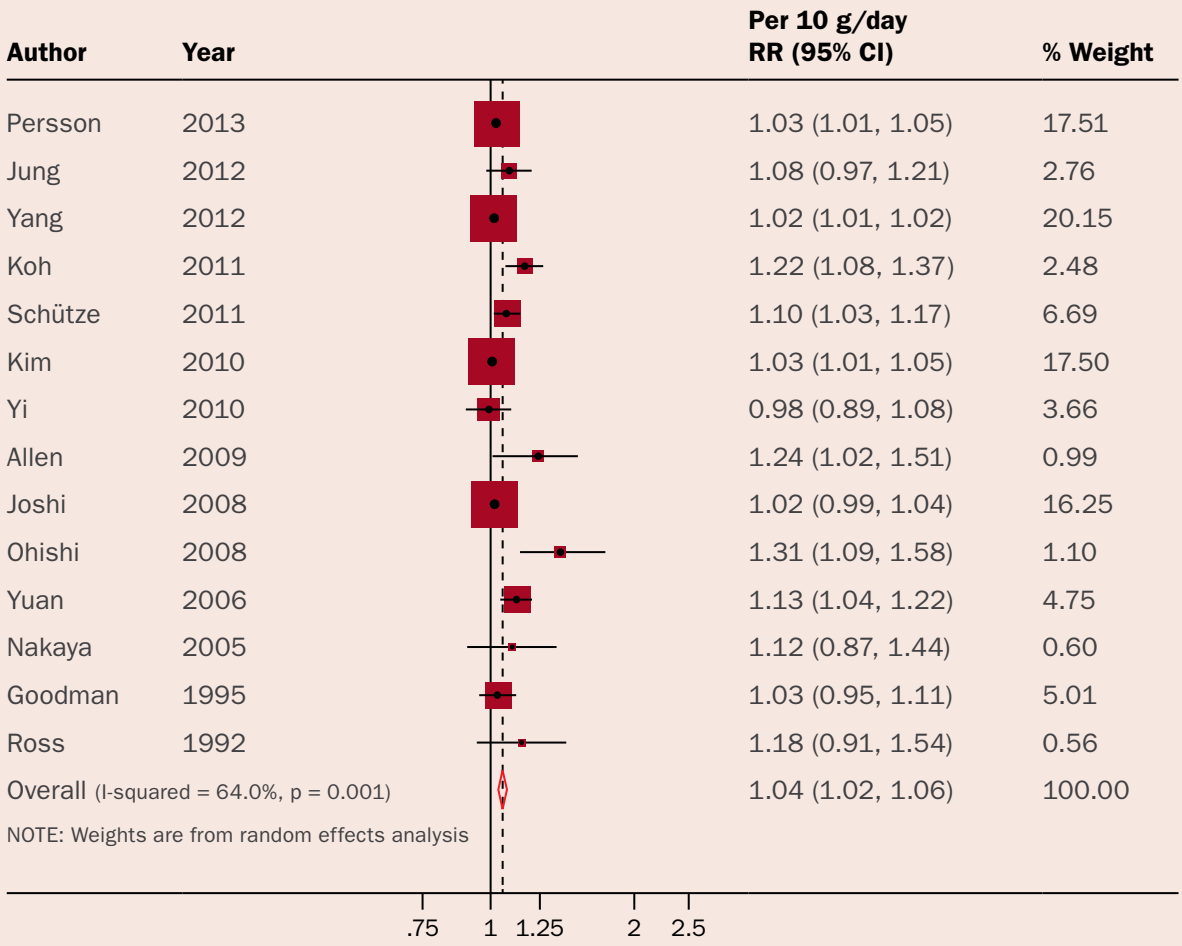
The observed association between consuming alcohol and liver cancer may be attenuated due to the exclusion of people who used to drink alcohol in five of 14 studies in the dose–response meta-analysis [105, 111, 113–115]. The CUP found a significant increased risk for people who used to drink alcohol compared with those who had never consumed alcohol (RR 2.58 [95% CI 1.76–3.77]; see CUP liver cancer SLR 2014, Figure 42).

Stratified analyses for the risk of liver cancer per 10 grams increase in alcohol (as ethanol) consumed per day were conducted for sex, geographic location and outcome.

When stratified by sex, a statistically significant increased risk was observed for men (RR 1.03 [95% CI 1.01–1.05]) and women (RR 1.19 [95% CI 1.04–1.35; see CUP liver cancer SLR 2014, Figure 37). When stratified by geographic location, a significant increased risk was observed in Asia (RR 1.04 [95% CI 1.02–1.07]; see CUP liver cancer SLR 2014, Figure 41). The finding for North America and Europe combined was similar but not statistically significant. When stratified by outcome, a significant increased risk was observed for incidence (RR 1.12 [95% CI 1.05–1.18]) and mortality (RR 1.02 [95% CI 1.01–1.03]; see CUP liver cancer SLR 2014, Figure 38).

There was no evidence of a non-linear dose–response relationship (p = 0.25). However, the increased risk of liver cancer became higher at intakes above 40 grams of alcohol (as ethanol) consumed per day and was statistically significant for intakes ≥ 45 grams of alcohol (as ethanol) per day (see **Figure 5.9** and **Table 5.9**).

Figure 5.8: CUP dose–response meta-analysis[1] for the risk of liver cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Persson, 2013 [104]; Jung, 2012 [105]; Yang, 2012 [106]; Koh, 2011 [107]; Schütze, 2011 [108]; Kim, 2010 [71]; Yi, 2010 [109]; Allen, 2009 [74]; Joshi, 2008 [110]; Ohishi, 2008 [111] Yuan, 2006 [112]; Nakaya, 2005 [113]; Goodman, 1995 [114]; Ross, 1992 [115].

For the non-linear analysis, studies that reported only continuous values or studies that used three categories of intake or fewer were excluded (eight studies were included).

Most studies included in the dose–response meta-analysis adjusted for tobacco smoking. Few studies adjusted for hepatitis B and C virus infection status.

A separate dose–response meta-analysis by type of alcoholic drink consumed was conducted for sake, but not for other types of drinks. The results for sake were similar to those for all types of drinks (RR 1.03 [95% CI 1.00–1.05] per 10 grams of alcohol (as ethanol) consumed per day; see CUP liver cancer SLR 2014, Figure 47).

[1] Five studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP liver SLR 2014, Table 41.

Figure 5.9: CUP non-linear dose-response association alcohol (as ethanol) intake and the risk of liver cancer

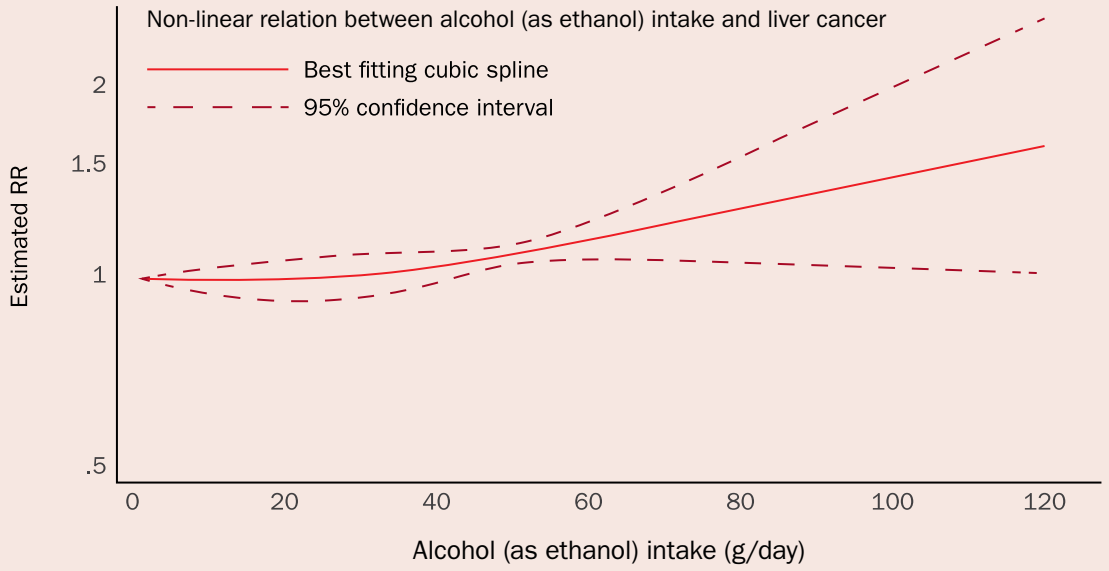


Table 5.9: CUP non-linear dose–response estimates of alcohol (as ethanol) intake and the risk of liver cancer

Alcohol (as ethanol) intake (g/day)	RR (95% CI)
0	1.00
12.5	0.99 (0.94–1.05)
20	0.99 (0.92–1.07)
45	1.06 (1.01–1.11)
55	1.11 (1.06–1.15)
75	1.23 (1.07–1.41)

5.1.3.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.10**) and one other published meta-analysis on consumption of alcohol and liver cancer were identified. The pooled analysis of four Japanese cohort studies reported an increased risk per 10 grams increase in alcohol (as ethanol) consumed per day, but this was statistically significant only in men [116].

The published meta-analysis of seven cohort studies reported no significant association between alcohol (as ethanol) and the risk of liver cancer when comparing the highest with the lowest levels consumed (RR 1.00 [95% CI 0.85–1.18]) [101].

An additional CUP meta-analysis of 17 studies (n = 6,372) – which included the four studies from the pooled analysis of Japanese cohort studies [116] and 13 additional studies from the CUP – showed a statistically significant four per cent increased risk of liver cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.04 [95% CI 1.02–1.06]).

Table 5.10: Summary of published pooled analyses of alcohol (as ethanol) intake and the risk of liver cancer

Publication	Increment	Sex	RR (95% CI)	No. studies (cohort)	No. cases
Pooled analysis of Japanese cohort studies [116]	10 g/day	Men	1.02 (1.004–1.04)	4	605
		Women	1.11 (0.96–1.29)	4	199

5.1.3.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The metabolism of alcohol (ethanol) in the liver leads to the production of acetaldehyde, a genotoxic and carcinogenic metabolite of alcohol metabolism. Higher ethanol consumption can also induce oxidative stress, inflammation and lipid peroxidation – all mechanisms that can promote cancer development [94]. Alcohol may also serve as a solvent for environmental carcinogens and impede DNA repair mechanisms [95], though evidence supporting this mechanism in the liver specifically are lacking. Evidence from animal studies suggests that in people who consume a large amount of alcohol, the hepatotoxic effects of alcohol may be compounded by the effect of malnutrition or poor dietary habits [117]. More recent research has focused on the impact of *chronic* high alcohol intake on dysbiosis of the gut microbiome and weakened gut barrier function [118]. Higher exposure to bacterial products leaked from the gut lumen has been observed to be associated with higher risk of liver cancer development [119], presumably by inducing chronic inflammation in the liver.

5.1.3.4 CUP Panel's conclusion

The evidence was consistent, and dose–response meta-analyses showed a statistically significant increased risk of liver cancer with higher alcohol consumption. This increased risk was still apparent when stratified by outcome and sex. There was evidence of high *heterogeneity*, but this appeared to be mainly due to the size of the effect. The results were consistent with findings from a published *pooled analysis*.

There was no evidence of a non-linear dose–response relationship. However, there was a statistically significant increased risk above intakes of about 45 grams of alcohol (as ethanol) per day. No conclusion was possible for intakes below 45 grams of alcohol (as ethanol) per day.

There is also evidence of plausible mechanisms operating in humans. Alcohol is a known cause of *cirrhosis* and a known *carcinogen*.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a convincing cause of liver cancer. This is based on evidence for alcohol intakes above about 45 grams per day (about three drinks a day).**

5.1.4 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.12 and CUP colorectal cancer SLR 2016: Sections 3.7.1 and 5.4.)

5.1.4.1 CUP dose–response meta-analyses

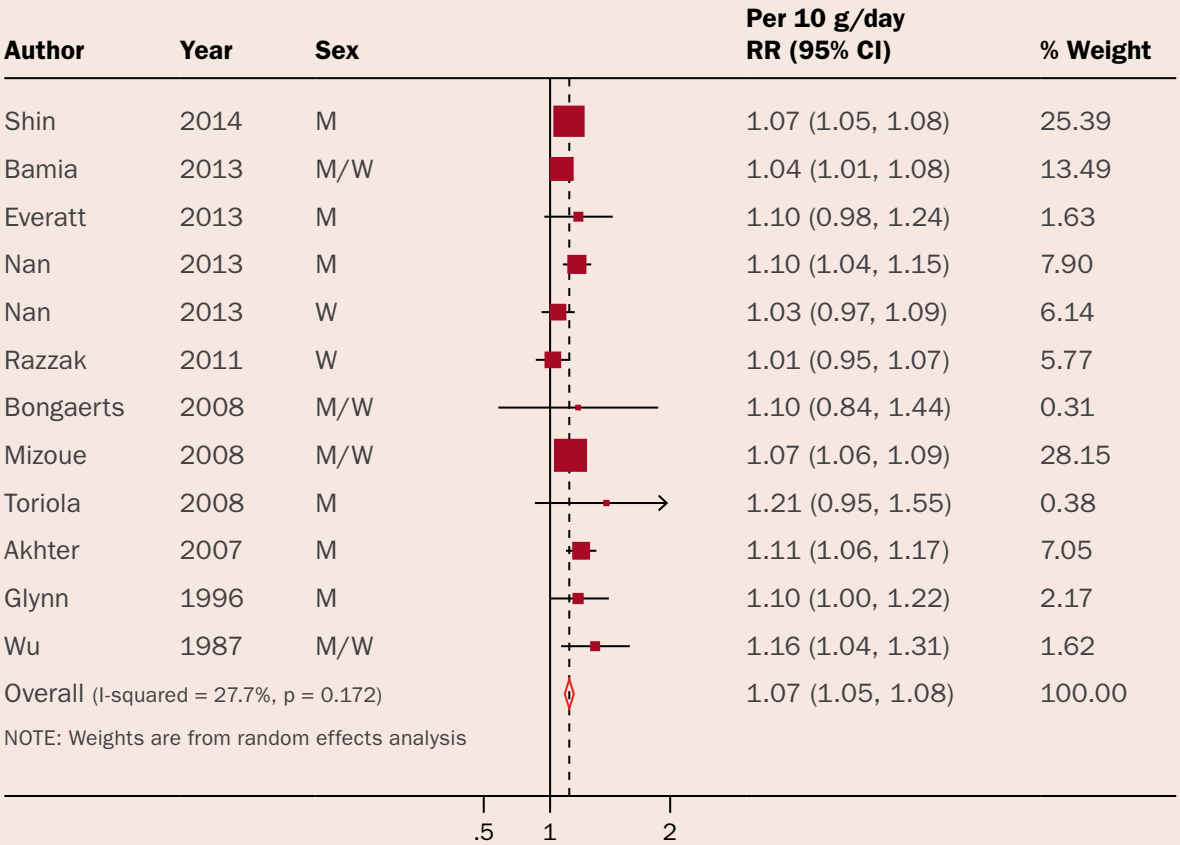
Sixteen of 19 identified studies were included in the dose–response meta-analysis, which showed a statistically significant seven per cent increased risk of colorectal cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.07 [95% CI 1.05–1.08]; n = 15,896) (see **Figure 5.10**). Low *heterogeneity* was observed (I^2 = 28%), and there was no evidence of small study bias with *Egger's test* (p = 0.33).

Stratified analyses for the risk of colorectal cancer per 10 grams increase in alcohol (as ethanol) consumed per day were conducted for sex, geographic location and cancer type.

When stratified by sex, a statistically significant increased risk was observed in men (RR 1.08 [95% CI 1.06–1.09]) but not women (RR 1.04 [95% CI 1.00–1.07]; see CUP colorectal cancer SLR 2016, Figure 390). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.05 [95% CI 1.02–1.08]), North America (RR 1.06 [95% CI 1.01–1.12]) and Asia (RR 1.07 [95% CI 1.06–1.08]; see CUP colorectal cancer SLR 2016, Figure 391). When stratified by cancer type, a significant increased risk of colorectal cancer was observed for colon (RR 1.07 [95% CI 1.05–1.09]) and rectal cancer (RR 1.08 [95% CI 1.07–1.10]). A significant increased risk was also observed in analyses stratified by sex in both colon (men: RR 1.08 [95% CI 1.06–1.10], women: RR 1.05 [95% CI 1.02–1.09]) and rectal cancer (men: 1.09 [95% CI 1.06–1.12], women: RR 1.09 [95% CI 1.04–1.15]) (see CUP colorectal cancer report 2017, Table 32 and CUP colorectal cancer SLR 2016, Figures 396, 398, 402 and 404).

When stratified by type of alcoholic drink, a significant increased risk was observed for wine (RR 1.04 [95% CI [1.01–1.08], colorectal or colon cancer), beer (RR 1.08 [95% CI 1.05–1.11], colorectal cancer) and spirits (RR 1.08 [95% CI 1.02–1.14], colorectal cancer) (see CUP colorectal cancer report 2017, Table 33 and CUP colorectal cancer SLR 2016, Figures 407, 409 and 411, respectively).

Figure 5.10: CUP dose–response meta-analysis[1] for the risk of colorectal cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Shin, 2014 [120]; Bamia, 2013 [121]; Everatt, 2013 [87]; Nan, 2013 [122]; Razzak, 2011 [123]; Bongaerts, 2008 [124]; Mizoue, 2008 [125]; Toriola, 2008 [126]; Akhter, 2007 [127]; Glynn, 1996 [128]; Wu, 1987 [129].

[1] A total of 16 studies was analysed in the CUP dose–response meta-analysis. The figure includes one pooled analysis of five studies [125] and Nan 2013 [122] reported separate RRs for two studies in a single publication.

There was evidence of a non-linear dose–response relationship (p = 0.01; see **Figure 5.11**). No significant increase in risk was observed at low intake levels (up to 20 grams of alcohol [as ethanol] per day; see **Table 5.11**). Significant increased risks were observed for 30 grams of alcohol (as ethanol) per day and above, where the relationship was positive and appeared linear (see CUP colorectal cancer SLR 2016, Figure 392).

Most studies included in the dose–response meta-analysis adjusted for tobacco smoking, BMI and diet (for example red meat), and some adjusted for physical activity. One study adjusted for age only [129]. Some studies adjusted for MHT use in postmenopausal women. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 218.

Separate dose–response meta-analyses conducted on alcoholic drinks (per one drink increase per day) showed no significant association between alcoholic drinks and colorectal, colon or rectal cancer (see CUP colorectal cancer report 2017, Table 35).

Figure 5.11: CUP non-linear dose–response association of alcohol (as ethanol) intake and the risk of colorectal cancer

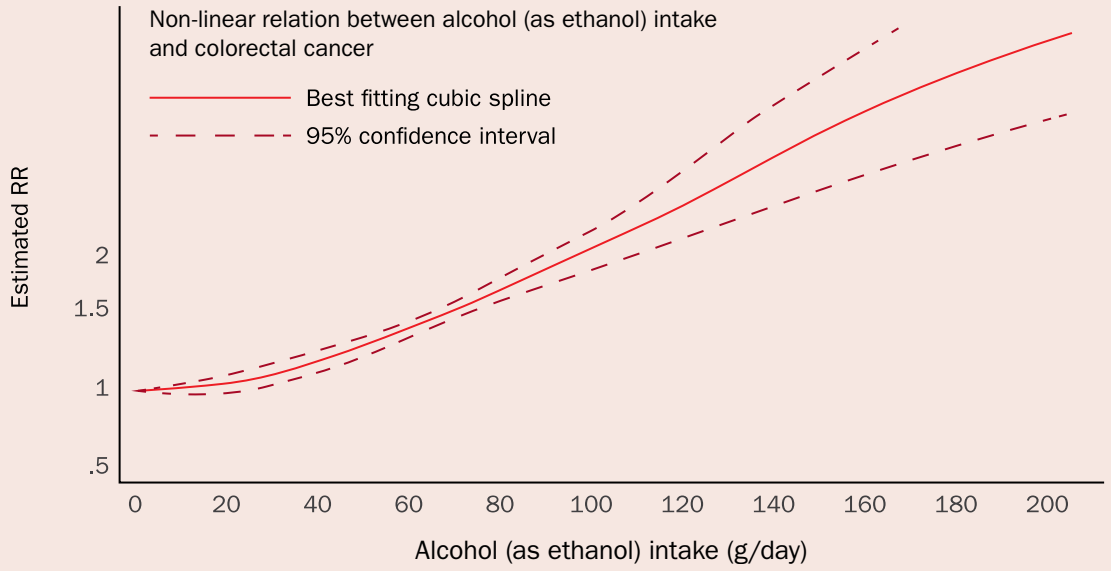


Table 5.11: CUP non-linear dose–response estimates of alcohol (as ethanol) intake and the risk of colorectal cancer

Alcohol (as ethanol) intake (g/day)	RR (95% CI)
0	1.00
10	1.02 (0.98–1.07)
20	1.07 (1.00–1.16)
30	1.15 (1.06–1.26)
40	1.25 (1.14–1.36)
50	1.41 (1.31–1.52)
60	1.60 (1.51–1.69)

Table 5.12: Summary of published pooled analyses of alcohol (as ethanol) intake and the risk of colorectal cancer

Publication	Increment	Sex	RR (95% CI)	No. studies (cohort)	No. cases
UK Dietary Cohort Consortium [130]	≥ 45 g ethanol/day vs 0 g ethanol/day	Men	1.24 (0.69–2.22)	7	266
		Women	1.52 (0.56–4.10)		313

5.1.4.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* on the consumption of alcohol (as ethanol) and the risk of colorectal cancer were identified. One [125] was included in the CUP dose–response meta-analysis and the other is shown in **Table 5.12**. No other published meta-analyses have been identified.

5.1.4.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The mechanisms of action for an effect of *chronic* alcohol consumption on colorectal cancer development appear to be diverse and are not well elucidated. Acetaldehyde, a toxic metabolite of ethanol oxidation, can be carcinogenic to colonocytes [92]. Higher ethanol consumption can also induce oxidative stress through increased production of reactive oxygen species that are genotoxic and carcinogenic [94]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism or interfere with retinoid metabolism and DNA repair mechanisms [95]. More recent research has focused on the impact of chronic high alcohol intake on dysbiosis of the gut microbiome and weakened gut barrier function [131]. Higher exposure to bacterial products leaked from the gut lumen has been observed to be associated with higher risk of developing colorectal cancer [132].

5.1.4.4 CUP Panel's conclusion

The evidence was consistent, and dose–response meta-analysis showed a statistically significant increased risk of colorectal cancer with increasing alcohol consumption, with low *heterogeneity*. The increased risk for consumption of alcohol was still apparent when stratified by geographic location and specific cancer site, as a statistically significant increased risk was observed for colorectal, colon and rectal cancers.

There was evidence of a non-linear association for colorectal cancer, with a significant increased risk for intakes of 30 grams of alcohol (as ethanol) per day and above.

The CUP findings were supported by one published pooled analysis, included in the CUP dose–response meta-analysis, which reported a significant increased risk for both men and women across all cancer sites. Another published pooled analysis reported no significant association. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a convincing cause of colorectal cancer. This is based on evidence for intakes above 30 grams per day (about two drinks a day).**

5.1.5 Breast (postmenopause)

(Also see CUP breast cancer report 2017: Section 7.5 and CUP breast cancer SLR 2017: Section 5.4.1.)

5.1.5.1 CUP dose–response meta-analyses

Twenty-two of 34 identified studies were included in the dose–response meta-analysis, which showed a statistically significant nine per cent increased risk of postmenopausal breast cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.09 [95% CI 1.07–1.12]; n = 35,221) (see **Figure 5.12**).

Figure 5.12: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 10 grams increase in alcohol (as ethanol) consumed per day

Source: Fagherazzi, 2015 [135]; Brinton, 2014 [136]; Falk, 2014 [137]; Park, 2014 [138]; Couto, 2013 [139]; Hartz, 2013 [134]; Sczaniecka, 2012 [133]; Chen, 2011 [140]; Suzuki, 2010 [141]; Trichopoulou, 2010 [142]; Ericson, 2009 [143]; Nielsen 2008 [144]; Zhang, 2007 [145]; Mellemkjaer, 2006 [146]; Suzuki, 2005 [147]; Horn-Ross, 2004 [148]; Petri, 2004 [149]; Sellers, 2004 [150]; Feigelson, 2003 [151]; Rohan, 2000 [152]; van den Brandt, 1995 [153]; Barrett-Connor, 1993 [154].

[1] Twelve studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP breast cancer SLR 2017, Table 265.

High *heterogeneity* was observed (I^2 = 71%). There was evidence of small study bias with *Egger's test* (p = 0.05), with two studies [133, 134] appearing as outliers (see CUP breast cancer SLR 2017, Figure 338).

Stratified analyses for the risk of postmenopausal breast cancer per 10 grams increase in alcohol (as ethanol) consumed per day were conducted for geographic location, MHT use and hormone receptor status, see CUP breast cancer report 2017, Table 8. For details of other stratified analyses that have been conducted, see CUP breast cancer SLR 2017, Section 5.4.1.

When stratified by geographic location, a statistically significant increased risk was observed in Europe (RR 1.08 [95% CI 1.04–1.12]) and North America (RR 1.11 95% CI 1.07–1.15]; see CUP breast cancer SLR 2017, Figure 340). When stratified by MHT use, a statistically significant increased risk was observed for women currently receiving MHT (RR 1.12 95% CI 1.09–1.15]) and those who had never received MHT (RR 1.04 [95% CI 1.02–1.07]) (see CUP breast cancer SLR 2017, Figure 345). When stratified by hormone receptor status, a significant increased risk was observed for women with *oestrogen*-receptor-positive (joint ER-positive and PR-positive tumours (1.06 [95% CI 1.03–1.09]) and for joint ER-positive and PR-negative tumours (RR 1.12 [95% CI 1.01–1.24]) (see CUP breast cancer SLR 2017, Figure 344), but not oestrogen-receptor-negative (joint ER-negative and PR-negative) tumours.

Separate dose–response meta-analyses of the risk of postmenopausal breast cancer, per 10 grams increase in alcohol (as ethanol) consumed per day, were also conducted for beer, wine and spirits. A significant increased risk was observed for wine (RR 1.12 [95% CI 1.08–1.17]), but not for beer or spirits (see CUP breast cancer report 2017, Table 10 and CUP breast cancer SLR 2017, Sections 5.4.1.1, 5.4.1.2 and 5.4.1.3).

There was no evidence of a non-linear dose–response relationship (p = 0.08). The dose–response was driven mainly by observations for intakes below 45 grams of alcohol (as ethanol) per day. Only one study reported higher levels of consumption [149] (see CUP breast cancer SLR 2017, Figure 334).

Most studies included in the dose–response meta-analysis adjusted for the main risk factors including BMI, tobacco smoking, family history of breast cancer, age at *menarche*, parity and MHT use. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 264.

5.1.5.2 Published pooled analyses and meta-analyses

Four published *pooled analyses* on the consumption of alcohol and the risk of postmenopausal breast cancer were identified. See **Table 5.13** for three of these analyses. No other published meta-analyses have been identified.

The most recent pooled analysis from the Pooling Project of Prospective Studies on Diet and Cancer [155] was not included in the main CUP analysis because it was published after the end of the CUP search. This study and the second pooled analysis [156] both reported a statistically significant increased risk per 10 grams increase in alcohol (as ethanol) consumed per day. The third pooled analysis [157] reported a significant increased risk in

both women who had given birth (parous) and those who had not (nulliparous) in a highest versus lowest meta-analysis. The fourth pooled analysis [158] (not shown in **Table 5.13**, as it reported absolute risk) reported a significant increased risk of postmenopausal breast cancer in women who had not used MHT in a highest versus lowest analysis.

The Pooling Project of Prospective Studies on Diet and Cancer analysis was also included in a separate CUP meta-analysis (with nine non-overlapping studies from the CUP) which showed a statistically significant 11 per cent increased risk of postmenopausal breast cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.11 [1.06–1.16]), see CUP breast cancer SLR 2017, Figure 337).

5.1.5.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The mechanism(s) whereby alcohol may increase the risk of breast cancer remains uncertain. Alcohol is metabolised hepatically and can influence the functional state of the liver and its ability to metabolise other nutrients, non-nutritive dietary factors and many host *hormones*. Thus, the potential mechanisms affecting breast *carcinogenesis* are diverse. Alcohol can also be metabolised in breast tissue to acetaldehyde, producing reactive oxygen species associated with DNA damage [3]. Alcohol may increase circulating levels of oestrogen, which is an established risk factor for breast cancer [159]. Alcohol may also act as a solvent, potentially enhancing the penetration of *carcinogens* into cells, which may be particularly relevant to tissues exposed to alcohol. People who consume large amounts of alcohol may have diets deficient in essential nutrients such as folate, rendering breast tissue susceptible to carcinogenesis.

Table 5.13: Summary of published pooled analyses of alcohol (as ethanol) intake and the risk of postmenopausal breast cancer

Publication	Increment/ contrast	Life events	RR (95% CI)	No. cohort studies	No. cases
Pooling Project of Prospective Studies on Diet and Cancer [155][1]	10 g/day		1.09 (1.07–1.11)	20	24,511
UK Dietary Cohort Consortium [156]	10 g/day		1.09 (1.01–1.18)	4	656
National Cancer Institute studies [157]	≥ 7 drinks/ week vs none	Nulliparous women, postmenopausal	1.30 (1.11–1.52)	4	1,501
		Parous women aged < 25 years at first birth	1.22 (1.11–1.35)		4,719
		Parous women aged ≥ 25 years at first birth	1.33 (1.19–1.50)		2,856

[1] Published after the CUP 2017 SLR search.

5.1.5.4 CUP Panel's conclusion

For postmenopausal breast cancer, the evidence was consistent, and the dose–response meta-analysis showed a significant increased risk with increasing alcohol consumption. Significant increased risk was shown for Europe and North America, for those who were currently using MHT, for those who had never used MHT and for patients with tumours that were ER-positive and PR-positive, and ER-positive and PR-negative.

The CUP analyses were supported by four published *pooled analyses*. When the most recent pooled analysis was combined with non-overlapping studies from the CUP, the observed increased risk remained significant. No threshold for alcohol intake was identified. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a convincing cause of postmenopausal breast cancer.**

5.1.6 Stomach

(Also see CUP stomach cancer report 2016: Section 7.5 and CUP stomach cancer SLR 2015: Sections 5.4.1).

5.1.6.1 CUP dose–response meta-analyses

Twenty-three of 30 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of stomach cancer and consumption of alcoholic drinks (RR 1.02 [95% CI 1.00–1.04]; per 10 grams increase in alcohol [as ethanol] consumed per day; n = 11,926) (see **Figure 5.13**).

Moderate *heterogeneity* was observed (I^2 = 39%). The meta-analysis became statistically significant when one study that reported exceptionally high intakes of alcohol (highest category of more than 34 units of alcohol per day) was removed [96] (RR 1.03 [95% CI 1.01–1.04], per 10 grams increase in alcohol (as ethanol) consumed per day).

There was evidence of small study bias with *Egger's test* (p = 0.03). Inspection of the funnel plot showed that small studies with risk estimates of less than 1.03 may be missing (CUP stomach cancer SLR 2015, Figure 130).

Stratified analyses for the risk of stomach cancer per 10 grams increase in alcohol (as ethanol) consumed per day were conducted for sex, geographic location, cancer subtype and history of tobacco smoking. For details of other stratified analyses that have been conducted, see CUP stomach cancer SLR 2015, Section 5.4.1.

When stratified by sex, a statistically significant increased risk was observed for men (RR 1.03 [95% CI 1.01–1.05]), but not women (RR 1.02 [95% CI 0.90–1.15]; see CUP stomach cancer SLR 2015, Figure 131). When stratified by geographic location, a significant increased risk was observed in Asia (RR 1.03 [95% CI 1.01–1.04]), but not in Europe or North America (see CUP stomach cancer SLR 2015, Figure 135). When stratified by cancer subtype, no significant association was observed for either cardia or *non-cardia cancers* (see CUP stomach cancer SLR 2015, Figure 134).

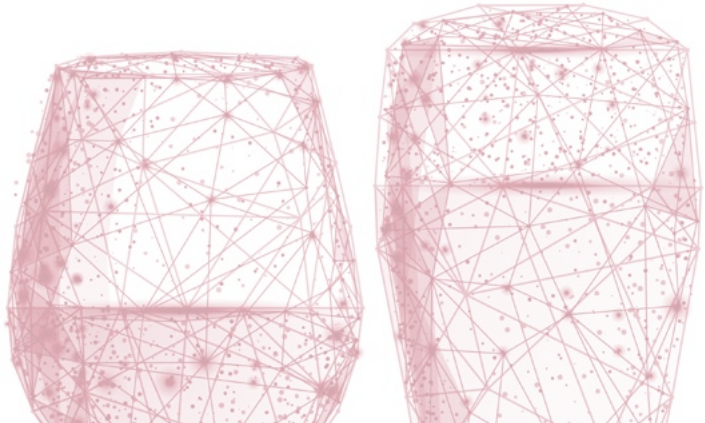
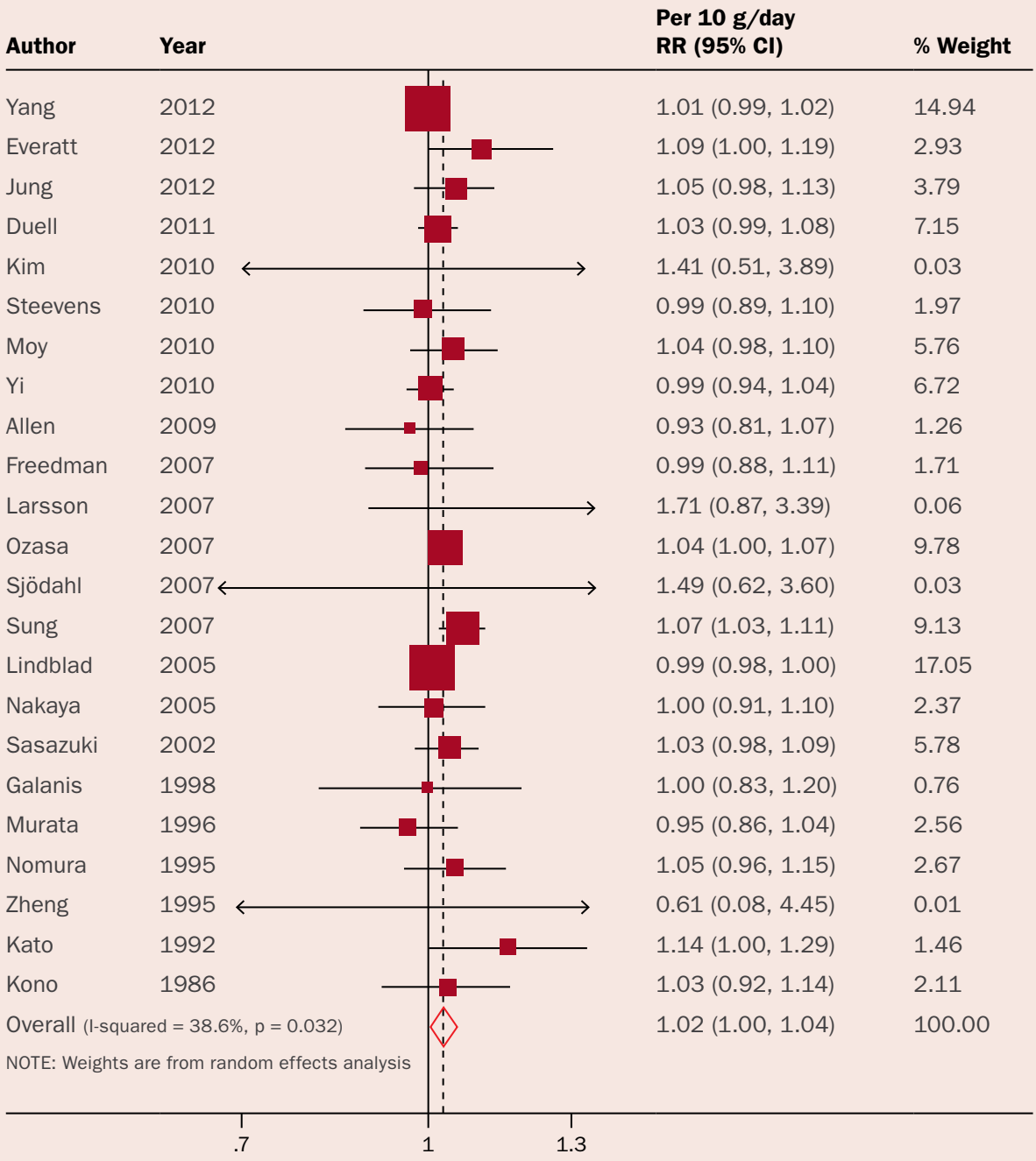


Figure 5.13: CUP dose–response meta-analysis for the risk of stomach cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Yang, 2012 [106]; Everatt, 2012 [160]; Jung, 2012 [105]; Duell, 2011 [161]; Kim, 2010 [71]; Steevens, 2010 [97]; Moy, 2010 [162]; Yi, 2010 [109]; Allen, 2009 [74]; Freedman, 2007 [99]; Larsson, 2007 [163]; Ozasa, 2007 [164]; Sjödahl, 2007 [165]; Sung, 2007 [166]; Lindblad, 2005 [96]; Nakaya, 2005 [113]; Sasazuki, 2002 [167]; Galanis, 1998 [168]; Murata, 1996 [169]; Nomura, 1995 [170]; Zheng, 1995 [171]; Kato, 1992 [172]; Kono, 1986 [173].

When stratified by history of tobacco smoking, a significant increased risk of stomach cancer was observed for the highest compared with the lowest level of alcohol consumed in people who had never smoked (RR 1.23 [95% CI 1.03–1.46]) as well as for those who smoke or used to smoke (RR 1.84 [95% CI 1.43–2.36]; see CUP stomach cancer SLR 2015, Figure 139).

There was no evidence of a non-linear dose–response relationship (p = 0.32). However, non-linear analysis showed that the linear dose–response association was statistically significant for 45 grams of alcohol (as ethanol) consumed per day and above (see **Figure 5.14** and **Table 5.14**).

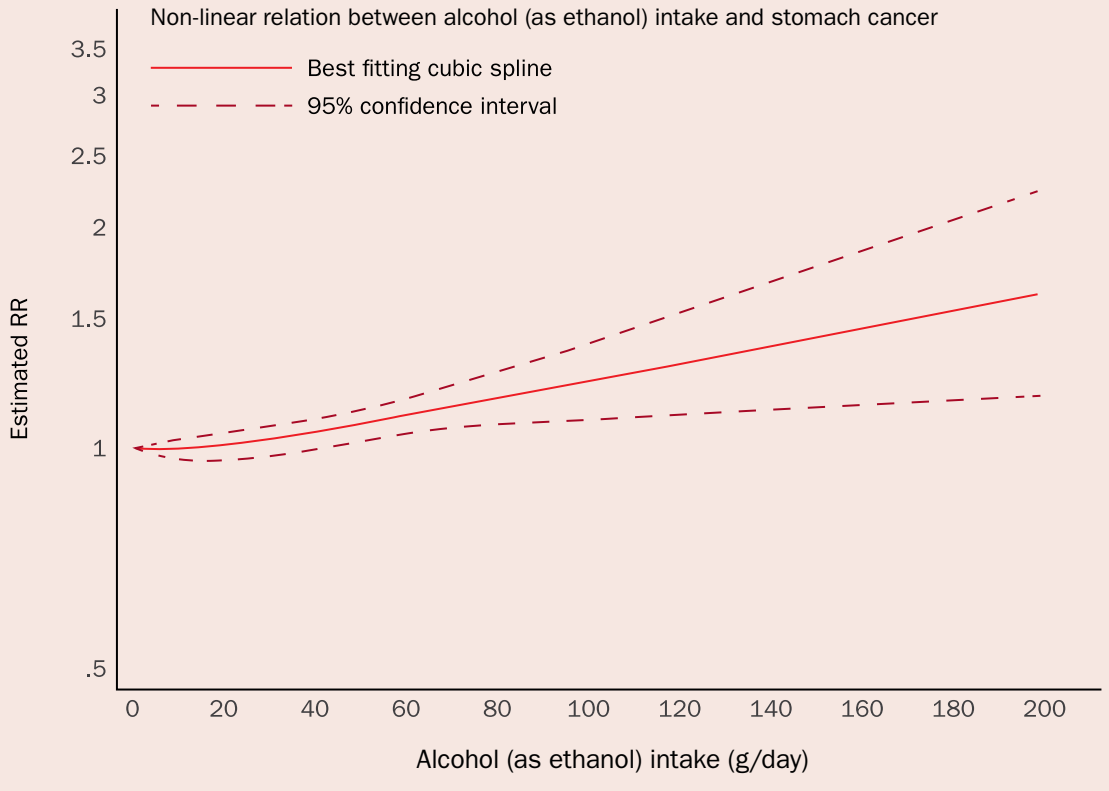
All studies included in the dose–response meta-analysis adjusted for age, sex and tobacco smoking. No study adjusted for *H. pylori* status. One study [96] reported an exceptionally high level of alcohol intake (more than 34 units of alcohol per day), and the estimate for this category was excluded from the non-linear meta-analysis. For information on the *adjustments* made in individual studies, see CUP stomach cancer SLR 2015, Table 110.

Separate dose–response meta-analyses for the risk of stomach cancer, per one drink increase per day, were also conducted for beer, wine and spirits. A statistically significant increased risk of stomach cancer was observed for consumption of beer (RR 1.08 [95% CI 1.01–1.16]), but not for consumption of wine or spirits (see CUP stomach cancer SLR 2015, Figures 142, 147 and 152).

Table 5.14: CUP non-linear dose–response estimates of alcohol (as ethanol) intakes and the risk of stomach cancer

Alcohol (as ethanol) intake (g/day)	RR (95% CI)
0	1.00
10	1.00 (0.98–1.03)
22	1.01 (0.97–1.06)
32	1.03 (0.98–1.08)
45	1.06 (1.01–1.11)
53	1.08 (1.03–1.13)
58	1.09 (1.04–1.14)
71	1.13 (1.05–1.21)
80	1.15 (1.06–1.26)
90	1.19 (1.07–1.32)
106	1.24 (1.08–1.42)
120	1.28 (1.08–1.52)

Figure 5.14: CUP non-linear dose–response association of alcohol (as ethanol) intake and the risk of stomach cancer



5.1.6.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis of 15 cohort studies on consumption of alcoholic drinks and the risk of stomach cancer has been identified [174]. It reported no statistically significant association for people who drink alcohol compared with people who do not (RR 1.04 [95% CI 0.97–1.11]).

5.1.6.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The precise mechanisms mediating the relationships between alcohol consumption and stomach cancer development are not completely understood. Alcohol consumption leads to exposure to acetaldehyde, the major and most toxic metabolite of alcohol. Acetaldehyde has been shown to disrupt DNA synthesis and repair [92]. Higher ethanol consumption also induces oxidative stress through increased production of reactive oxygen species, which are genotoxic and carcinogenic [94]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism or interfere with retinoid metabolism and with DNA repair mechanisms [95].

5.1.6.4 CUP Panel's conclusion

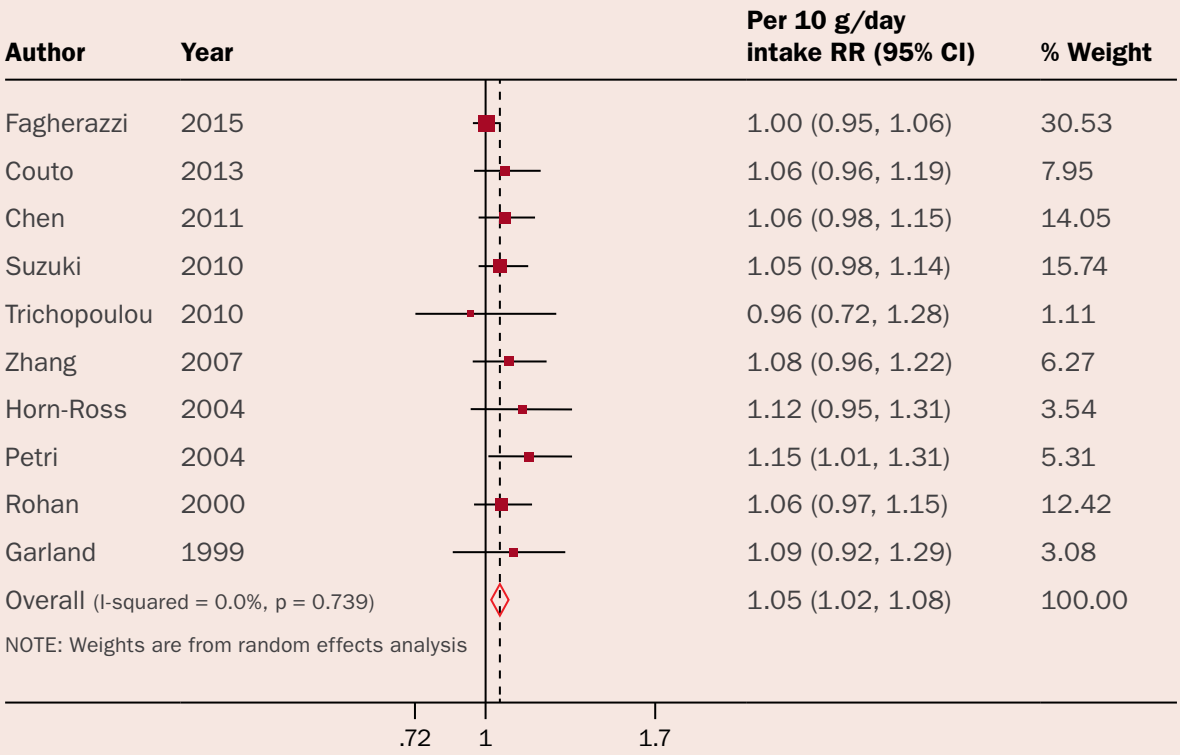
Overall, the evidence tended to show an increased risk of stomach cancer with greater consumption of alcohol. The dose–response meta-analysis was statistically significant when one study with exceptionally high (highest category more than 34 units per day) intakes of alcohol was excluded. Non-linear analysis showed that the dose–response association was significant at higher levels of alcohol intake (from 45 grams of ethanol per day). No conclusion was possible for intakes below 45 grams of alcohol (as ethanol) per day.

When stratified by sex, outcome, geographic region and tobacco smoking, the analyses showed a significant increased risk of stomach cancer in men, in cohorts in Asia, and in people who had never smoked and in those who smoke or used to smoke. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks probably increases the risk of stomach cancer. This is based on evidence for intakes greater than 45 grams per day (about three drinks a day).**

Figure 5.15: CUP dose–response meta-analysis[1] for the risk of premenopausal breast cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Fagherazzi, 2015 [135]; Couto, 2013 [139]; Chen, 2011 [140]; Suzuki, 2010 [141]; Trichopoulou, 2010 [142]; Zhang, 2007 [145]; Horn-Ross, 2004 [148]; Petri, 2004 [149]; Rohan 2000 [152]; Garland, 1999 [175].

5.1.7 Breast (premenopause)

(Also see CUP breast cancer report 2017: Section 7.5 and CUP breast cancer SLR 2017: Sections 5.4.1.)

5.1.7.1 CUP dose–response meta-analyses

Ten of 16 identified studies were included in the dose–response meta-analysis, which showed a statistically significant five per cent increased risk of premenopausal breast cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 1.05 [95% CI 1.02–1.08]; n = 4,227) (see **Figure 5.15**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.10).

A stratified analysis for the risk of premenopausal breast cancer, per 10 grams increase in alcohol (as ethanol) consumed per day, was conducted for geographic location. A statistically significant increased risk was observed in North America (RR 1.07 (95% CI 1.02–1.12); see CUP breast cancer SLR 2017, Figure 333), but not in Europe, Asia or Australia.

Please see CUP breast cancer SLR 2017, Section 5.4.1 for details of other stratified analyses that have been conducted.

Most studies included in the dose–response meta-analysis adjusted for BMI, tobacco smoking, family history of breast cancer, age at *menarche* and parity. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 260.

[1] Six studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP breast cancer SLR 2017, Table 261.

Separate dose–response meta-analyses on the risk of premenopausal breast cancer, per 10 grams increase in alcohol (as ethanol) consumed per day, were also conducted for beer, wine and spirits. A significant increased risk was observed for beer (RR 1.32 [95% CI 1.06–1.64]) but not for wine or spirits (see CUP breast cancer report 2017, Table 7 and CUP breast cancer SLR 2017, Sections 5.4.1.1, 5.4.1.2 and 5.4.1.3).

5.1.7.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.15**) on consumption of alcohol and the risk of premenopausal breast cancer was identified. No other published meta-analyses have been identified. The pooled analysis of 15 cohort studies reported no significant association per 10 grams increase in alcohol (as ethanol) per day and no differences by hormone receptor status [155].

The pooled analysis was not included in the CUP dose–response meta-analysis because it was published after the end of the CUP search. It was included in an additional CUP meta-analysis of 18 studies (n = 4,426) – which included the 15 studies from the Pooling Project of Prospective Studies on Diet and Cancer [155] and three non-overlapping studies from the CUP [135, 142, 149]. No significant association was observed; see CUP breast cancer SLR 2017, Figure 331.

5.1.7.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The mechanism or mechanisms whereby alcohol may increase risk of breast cancer remain uncertain. Alcohol is metabolised hepatically and can influence the functional state of the liver and its ability to metabolise other nutrients, non-nutritive dietary factors, and many host *hormones*. Thus, the potential mechanisms affecting breast *carcinogenesis* are diverse. Alcohol can also be metabolised in breast tissue to acetaldehyde, producing reactive oxygen species associated with DNA damage [3]. Alcohol may increase circulating levels of oestrogen which is an established risk factor for breast cancer [159]. Alcohol may also act as a solvent, potentially enhancing penetration of *carcinogens* into cells, which may be particular relevant to tissues particularly exposed to alcohol. People who consume large amounts of alcohol may have diets deficient in essential nutrients such as folate, rendering breast tissue susceptible to carcinogenesis.

Table 5.15: Summary of published pooled analyses of alcohol (as ethanol) intake and the risk of premenopausal breast cancer

Publication	Increment	RR (95% CI)	No. studies	No. cases
Pooling Project of Prospective Studies on Diet and Cancer[1] [155]	10 g/day	1.03 (0.99–1.08)	15	3,730

[1] Published after the CUP SLR 2017 search.

5.1.7.4 CUP Panel's conclusion

For premenopausal breast cancer, the evidence was generally consistent, and the dose–response meta-analysis showed a statistically significant increased risk with increasing alcohol consumption. No *heterogeneity* was observed. Significant increased risk was shown for North America.

A *pooled analysis* found no significant association for premenopausal breast cancer; when combined with non-overlapping studies from the CUP, an increased risk remained but it was not significant. No threshold for alcohol intake was identified. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks is a probably a cause of premenopausal breast cancer.**

5.1.8 Kidney

(Also see CUP kidney cancer report 2015: Section 7.2 and CUP kidney cancer SLR 2015: Section 5.4.1).

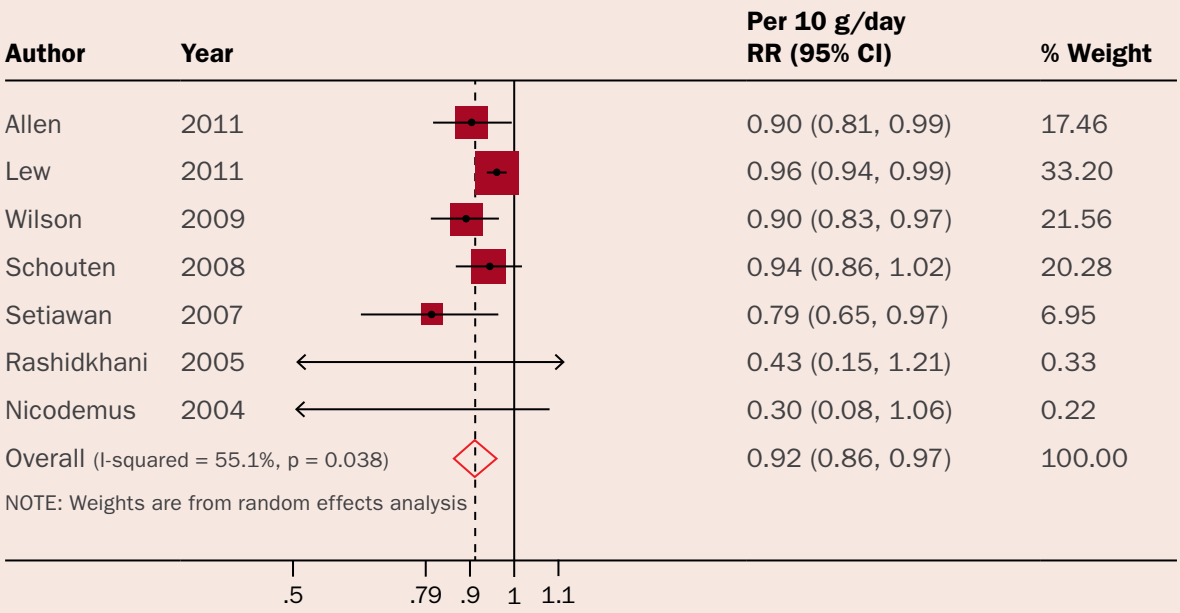
5.1.8.1 CUP dose–response meta-analyses

Seven of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant eight per cent decreased risk of kidney cancer per 10 grams increase in alcohol (as ethanol) consumed per day (RR 0.92 [95% CI 0.86–0.97]; n = 3,525) (see **Figure 5.16**).

High *heterogeneity* was observed (I^2 = 55%). The overall heterogeneity appeared to be explained by a smaller decrease in risk (compared with other studies) reported by one study, mainly for men [176]. The heterogeneity decreased after exclusion of this study (I^2 = 25%).

There was evidence of small study bias with *Egger's test* (p = 0.001). Two smaller studies [177, 178] found a greater decreased risk

Figure 5.16: CUP dose–response meta-analysis for the risk of kidney cancer, per 10 grams increase in alcohol (as ethanol) consumed per day



Source: Allen, 2011 [179]; Lew, 2011 [176]; Wilson, 2009 [180]; Schouten, 2008 [181]; Setiawan, 2007 [182]; Rashidkhani, 2005 [177], Nicodemus, 2004 [178].

than the other studies (see CUP kidney cancer SLR 2015, Figure 55). The highest category reported was 30 grams or more of alcohol (as ethanol) per day (see CUP kidney cancer SLR 2015, Figure 53). There was insufficient specific evidence on higher levels of alcohol consumption to assess the effect of alcohol intake at these levels on kidney cancer (see CUP kidney cancer SLR 2015, Figure 56).

A stratified analysis for the risk of kidney cancer per 10 grams increase in alcohol (as ethanol) consumption per day was conducted for sex. A statistically significant decreased risk was observed for women (RR 0.81 [95% CI 0.68–0.96]), but not men (RR 0.92 [95% CI 0.84–1.00]; see CUP kidney cancer report 2015, Table 2 and CUP kidney cancer SLR 2015, Figure 57).

There was no evidence of a non-linear dose–response relationship (p = 0.78).

All studies included in the dose–response meta-analysis apart from one (Rashidkhani 2005) adjusted for tobacco smoking.

Separate dose–response meta-analyses on the risk of kidney cancer, per 10 grams increase in alcohol (as ethanol) consumed per day, were also conducted for beer, wine and spirits. A significant decreased risk was observed for beer (RR 0.77 [95% CI 0.65–0.92], but not for wine or spirits (see CUP kidney SLR 2015, Figures 62, 65 and 68).

5.1.8.2 Published pooled analyses and meta-analyses

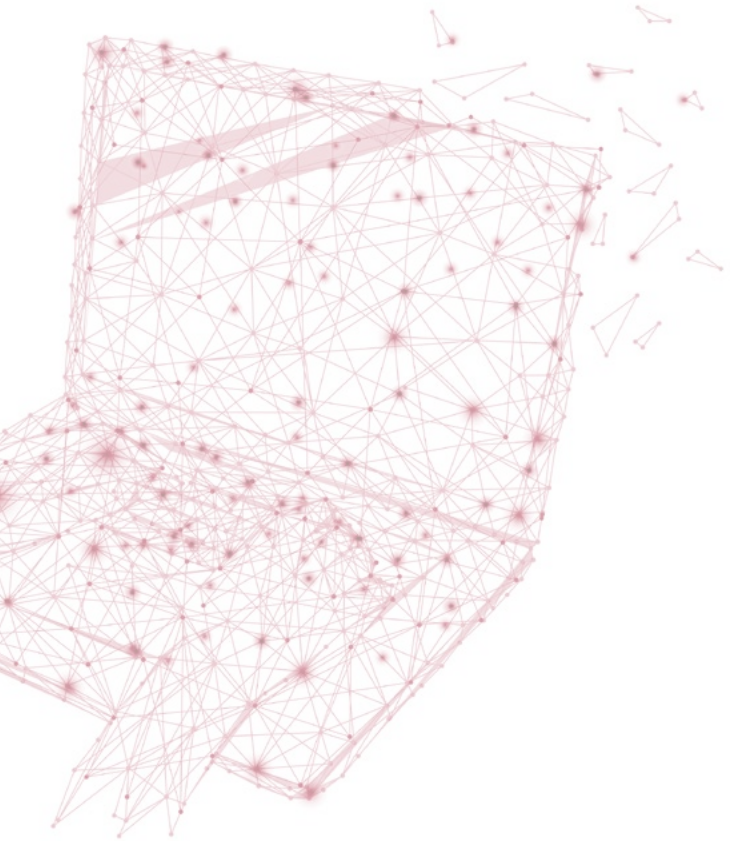
One published *pooled analysis* (see **Table 5.16**) and two other published meta-analyses on the consumption of alcohol and the risk of kidney cancer were identified. The pooled analysis of cohort studies reported a statistically significant decreased risk when comparing the highest with the lowest level of alcohol consumed, and the dose–response meta-analysis showed a significant 19 per cent decreased risk per 10 grams increase in alcohol (as ethanol) consumed per day [183].

Both published meta-analyses of cohort studies reported a significant decreased risk when comparing the highest with the lowest levels of alcohol intake [184, 185]. One showed a statistically significant 26 per cent decreased risk for an intake of 12.5 to 49.9 grams of alcohol (as ethanol) per day compared with no alcohol (RR 0.74 [95% CI 0.61–0.88]; n = 3,032) [184]. The other showed a 29 per cent decreased risk for the highest compared with the lowest level of alcohol consumed (RR 0.71 [95% CI 0.63–0.78]; n = 4,179) [185].

Table 5.16: Summary of pooled analyses of alcohol consumption and the risk of kidney cancer

Analysis	Increment/ contract	RR (95% CI)	No. studies	No. cases
Pooling Project of Prospective Studies on Diet and Cancer [183]	≥ 15 g/day vs no alcohol	0.72 (0.60–0.86)	12	1,430
	10 g/day[1]	0.81 (0.74–0.90)		

[1] Participants with intake > 30 grams per day were excluded.



An additional meta-analysis of 15 studies (n ≈ 4,179 [for the category ≥ 15 grams alcohol (as ethanol) per day]) – which included 12 studies from the Pooling Project of Prospective Studies on Diet and Cancer [183] and three non-overlapping studies from the CUP [176, 179, 182] – showed a statistically significant 12 per cent decreased risk per 10 grams increase in alcohol (as ethanol) consumed per day (RR 0.88 [0.79–0.97]); see CUP kidney cancer SLR 2015, Figure 59.

5.1.8.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The mechanisms that may explain the inverse relationship between moderate alcohol consumption and kidney cancer risk are uncertain but appear to be consistent for the various renal cancer subtypes [186]. Possible biological mechanisms proposed include improved blood lipid profiles among people who drink a moderate amount of alcohol and higher adiponectin levels [187, 188]. It has been suggested that the diuretic effects of alcohol may, in part, be responsible for lower kidney cancer risk among people who drink alcohol. However, inconsistent results for the consumption of other fluids, diuretics and risk of kidney cancer do not support this hypothesis [189].

5.1.8.4 CUP Panel's conclusion

The evidence for a decreased risk of kidney cancer with alcohol consumption was generally consistent. There was evidence of *heterogeneity*, which appeared to be due to differences in the size of the effect. When stratified by sex, the decreased risk of kidney cancer was significant for women but not for men. The results were consistent with findings from a published *pooled analysis*. The protective effect was apparent up to 30 grams of alcohol (as ethanol) per day (about two drinks a day). There was insufficient evidence beyond 30 grams of alcohol (as ethanol) per day. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **Consumption of alcoholic drinks probably protects against kidney cancer. This is based on evidence for alcohol intakes up to 30 grams per day (about two drinks a day).**

6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that alcohol is a cause of five cancers (mouth, pharynx and larynx; oesophagus; liver; colorectum and breast). The evidence for all of those cancers has remained strong. There is new strong evidence that alcohol is probably a cause of stomach cancer, bringing the total to six cancers. With the use of non-linear dose–response analysis it has been possible to identify thresholds for some cancers, the increased risk of cancer is apparent above 30 grams of alcohol (as ethanol) per day for colorectal cancer and above 45 grams per day for stomach and liver cancers.

The 2007 report found that ethanol itself was the causal factor (based on epidemiology and mechanisms). The relationships between drinking alcohol and different cancers were largely unaffected by the type of alcoholic drink consumed. This finding is generally upheld.

Evidence for oesophageal cancer, which is now considered by subtype in the CUP, supports the conclusion that consuming alcohol is a convincing cause of *squamous cell carcinoma* but not of *adenocarcinoma*.

As in 2007, current evidence does not identify a generally 'safe' threshold for consumption of alcoholic drinks for breast cancer (pre and postmenopause) and oesophageal cancer (squamous cell carcinoma). That is, there does not seem to be a threshold below which an effect on cancer risk is not observed.

In 2007, the Panel considered the evidence on kidney cancer and alcoholic drinks was sufficient to judge that consuming alcoholic drinks was unlikely to have an adverse effect on the risk of kidney cancer and that the evidence was inadequate to draw a conclusion regarding a protective effect. Now the evidence is sufficient for the Panel to judge that consuming alcoholic drinks probably protects against kidney cancer (up to 30 grams of alcohol [as ethanol] a day).

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Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
ER-negative	Oestrogen-receptor negative
ER-positive	Oestrogen-receptor positive
H. pylori	*Helicobacter pylori*
MHT	Menopausal hormone therapy
NSCLC	Non-small-cell lung cancer
PR-negative	Progesterone-receptor negative
PR-positive	Progesterone-receptor positive
RR	Relative risk
SCLC	Small-cell lung cancer
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

Adenosquamous carcinoma
A type of cancer that contains two types of cells: squamous cells (thin, flat cells that line certain organs) and gland-like cells.

Adjustment
A statistical tool for taking into account the effect of known confounders (see **confounder**).

Antioxidant
A molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction involving the loss of electrons, which can produce free radicals. In turn, these radicals can start chain reactions, which can cause damage or death to cells (see **free radicals**).

Basal cell carcinoma
A type of cancer of the basal cells at the bottom of the epidermis. The most common form of skin cancer. Basal cell carcinomas are usually found on areas of the body exposed to the sun. They rarely metastasise (spread) to other parts of the body.

Body mass index (BMI)
Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m^2). Provides an indirect measure of body fatness.

Caecum
A pouch connected to the junction of the small and large intestines

Calcium
An essential nutrient for many regulatory processes in all living cells, in addition to playing a structural role in the skeleton. Calcium plays a critical role in the complex hormonal and nutritional regulatory network related to vitamin D metabolism, which maintains the serum concentration of calcium within a narrow range while optimising calcium absorption to support host function and skeletal health.

Carcinogen
Any substance or agent capable of causing cancer.

Carcinogenesis
The process by which a malignant tumour is formed.

Carcinoma
Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Cardia stomach cancer
A sub-type of stomach cancer that occurs in the cardia, near the gastro-oesophageal junction

Case-control study
An epidemiological study in which the participants are chosen on the basis of their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as tobacco smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cholangiocarcinoma
A malignant tumour in the ducts that carry bile from the liver to the small intestine.

Chronic
Describing a condition or disease that is persistent or long lasting.

Cirrhosis
A condition in which normal liver tissue is replaced by scar tissue (fibrosis), with nodules of regenerative liver tissue.

Clear cell renal cell carcinoma (CCRCC)
The most common type of kidney cancer in adults, characterised by malignant epithelial cells with clear cytoplasm.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, tobacco smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

Colon
Part of the large intestine extending from the caecum to the rectum.

Confidence interval (CI)
A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the association of tobacco smoking and relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% chance that the true value lies between 5 and 15.

Confounder/confounding factors
A variable that is associated with both an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that tobacco smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

Diet, nutrition and physical activity
In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

Dose–response
A term derived from pharmacology that describes the degree to which an association or effect changes as the level of an exposure changes, for instance, intake of a drug or food.

Effect modification
Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

Egger's test
A statistical test for small study effects such as publication bias.

Endocrine
Referring to organs or glands that secrete hormones into the blood.

Energy
Energy, measured as calories or joules, is required for all metabolic processes. Fats, carbohydrates, proteins and alcohol from foods and drinks release energy when they are metabolised in the body.

Epithelial (see **epithelium**)

Epithelium
The layer of cells covering internal and external surfaces of the body, including the skin and mucous membranes lining body cavities such as the lung, gut and urinary tract.

Exocrine
Relating to or denoting glands that secrete their products through ducts opening on to an epithelium rather than directly into the blood.

Exposure
A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

Familial
Relating to or occurring in a family or its members.

Forest plot
A simple visual representation of the amount of variation between the results of the individual studies in a meta-analysis. Their construction begins with plotting the observed exposure effect

of each individual study, which is represented as the centre of a square. Horizontal lines run through this to show the 95% confidence interval. Different-sized squares may be plotted for each of the individual studies, the size of the box increasing with the size of the study and the weight that it takes in the analysis. The overall summary estimate of effect and its confidence interval can also be added to the bottom of this plot, if appropriate, represented as a diamond. The centre of the diamond is the pooled summary estimate and the horizontal tips are the confidence intervals.

Free radicals
An atom or molecule that has one or more unpaired electrons. A prominent feature of radicals is that they have high chemical reactivity, which explains their normal biological activities and how they inflict damage on cells. There are many types of radicals, but those of most importance in biological systems are derived from oxygen and known collectively as reactive oxygen species.

Head and neck cancer
Includes cancers of the oral cavity, pharynx and larynx, nasal cavity and salivary glands.

***Helicobacter pylori* (*H. pylori*)**
A gram-negative bacterium that lives in the human stomach. It colonises the gastric mucosa and elicits both inflammatory and lifelong immune responses.

Hepatocellular carcinoma
Primary malignant tumour of the liver.

Heterogeneity
A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I^2 test.

High-income countries
As defined by the World Bank, countries with an average annual gross national income per capita of US$12,236 or more in 2016. This term is more precise than and used in preference to ‘economically developed countries’.

Hormone
A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

Hormone receptor status
Hormone receptors are proteins found in and on breast or other cells that respond to circulating hormones and influence cell structure or function. A cancer is called oestrogen-receptor-positive (ER+) if it has receptors for oestrogen, and oestrogen-receptor-negative (ER-) if it does not have the receptors for oestrogen.

Large cell carcinoma
A term used to describe a microscopically identified variant of certain cancers, for example, lung cancers, in which the abnormal cells are particularly large.

Melanoma
Malignant tumour of the skin derived from the pigment-producing cells (melanocytes).

Menarche
The start of menstruation.

Menopausal hormone therapy (MHT)
Treatment with oestrogens and progesterones with the aim of alleviating menopausal symptoms or osteoporosis. Also known as hormone replacement therapy.

Menopause
The cessation of menstruation.

Meta-analysis
The process of using statistical methods to combine the results of different studies.

Metastasis/metastatic spread
The spread of malignant cancer cells to distant locations around the body from the original site.

Mucinous carcinoma
A type of cancer that begins in cells that line certain internal organs and produce mucin (the main component of mucus).

Non-cardia stomach cancer
A subtype of stomach cancer that occurs in the lower portion of the stomach.

Non-communicable diseases (NCDs)
Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

Non-linear analysis
A non-linear dose–response meta-analysis does not assume a linear dose–response relationship between exposure and outcome. It is useful for identifying whether there is a threshold or plateau.

Obesity
Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m^2 or more. Different cut-off points have been proposed for specific populations.

Odds ratio
A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

Oestrogen
The female sex hormones, produced mainly by the ovaries during reproductive life and also by adipose tissue.

Papillary renal cell carcinoma
A type of cancer that forms inside the lining of the kidney tubules.

Policy
A course of action taken by a governmental body including, but not restricted to, legislation, regulation, guidelines, decrees, standards, programmes and fiscal measures. Policies have three interconnected and evolving stages: development, implementation, and evaluation. Policy development is the process of identifying and establishing a policy to address a particular need or situation. Policy implementation is a series of actions taken to put a policy in place, and policy evaluation is the assessment of how the policy works in practice.

Polymorphisms
Common variations (in more than one per cent of the population) in the DNA sequence of a gene.

Pooled analysis
In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Progesterone
Female sex hormone, produced mainly by the ovaries during reproductive life and by the placenta during pregnancy.

Rectum
The final section of the large intestine, terminating at the anus.

Relative risk (RR)
The ratio of the rate of an outcome (for example, disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Selection bias
Bias arising from the procedures used to select study participants and from factors influencing participation.

Squamous cell carcinoma
A malignant cancer derived from squamous epithelial cells.

Statistical power
The power of any test of statistical significance, defined as the probability that it will reject a false null hypothesis.

Transitional cell carcinomas
Cancer that develops in the lining of the renal pelvis, ureter or bladder.

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Appendix 1: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the 2007 Second Expert Report [1]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent *cohort studies*.
- No substantial unexplained *heterogeneity* within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including *confounding*, measurement error and *selection bias*.
- Presence of a plausible biological gradient ('*dose–response*') in the association. Such a gradient need not be linear or even in the same direction across the different levels of *exposure*, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five *case-control studies*.
- No substantial unexplained *heterogeneity* between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and *selection bias*.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of *adjustment* for known *confounders*) or by any combination of these factors.

When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (dietandcancerreport.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose–response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate *statistical power*. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- Presence of a plausible biological gradient ('*dose–response*') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2: Mechanisms

The evidence on mechanisms has been based on human and animal studies. Though not a systematic or exhaustive search, the expert reviews represent the range of currently prevailing hypotheses.

Alcoholic drinks

Mouth, pharynx and larynx

The precise mechanisms underlying the relationship between alcohol consumption and cancers of the mouth, pharynx, and larynx are not completely understood. A large body of experimental evidence has shown that acetaldehyde, the major and most toxic metabolite of alcohol, disrupts DNA synthesis and repair and thus may contribute to a carcinogenic cascade [92, 93]. Higher ethanol consumption also induces oxidative stress through increased production of reactive oxygen species, which are potentially genotoxic [94]. It is hypothesised that alcohol may also function as a solvent for cellular penetration of dietary or environmental (for example tobacco) carcinogens or interfere with DNA repair mechanisms [95]. High consumers of alcohol may also have diets that are lacking in essential nutrients, such as folate, rendering target tissues more susceptible to carcinogenic effects of alcohol.

Oesophagus (squamous cell carcinoma)

Several mechanisms have been proposed to explain the association of alcohol drinking with oesophageal *squamous cell carcinoma*. Alcohol consumption can induce the expression of Cytochrome P450 2E1 (CYP2E1) in the human oesophagus in a dose-dependent manner and CYP2E1 activity yields substantial quantities of reactive oxygen species that may cause carcinogenic DNA lesions through oxidative stress, inflammation and lipid peroxidation [103]. Acetaldehyde, the major alcohol metabolite, may promote *carcinogenesis* by inhibiting DNA methylation or interacting with retinoid metabolism, both of which regulate the transcription of genes that have a key role in cellular growth and differentiation [92]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism, or interfere with retinoid metabolism and with DNA repair mechanisms [95].

Liver

The metabolism of alcohol (ethanol) in the liver leads to the production of acetaldehyde, a genotoxic and carcinogenic metabolite of alcohol metabolism. Higher ethanol consumption can also induce oxidative stress, inflammation and lipid peroxidation – all mechanisms that can promote cancer development [94]. Alcohol may also serve as a solvent for environmental carcinogens and impede DNA repair mechanisms [95], though evidence supporting these mechanisms in liver specifically are lacking. Evidence from animal studies suggests that in people who consume a large amount of alcohol, the hepatotoxic effects of alcohol may be compounded by the effect of malnutrition or poor dietary habits [117]. More recent research has focused on the impact of *chronic* high alcohol intake on dysbiosis of the gut microbiome and weakened gut barrier function [118]. Higher exposure to bacterial products leaked from the gut lumen has been observed to be associated with higher risk of liver cancer development [119], presumably by inducing chronic inflammation in the liver.

Colorectum

The mechanisms of action for an effect of *chronic* alcohol consumption on colorectal cancer development appear to be diverse and are not well elucidated. Acetaldehyde, a toxic metabolite of ethanol oxidation, can be carcinogenic to colonocytes [92]. Higher ethanol consumption can also induce oxidative stress through increased production of reactive oxygen species that are genotoxic and carcinogenic [94]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism, or interfere with retinoid metabolism and DNA repair mechanisms [95]. More recent research has focused on the impact of chronic high alcohol intake on dysbiosis of the gut microbiome and weakened gut barrier function [131]. Higher exposure to bacterial products leaked from the gut lumen has been observed to be associated with higher risk of colorectal cancer development [132].

Breast (postmenopause)

The mechanism or mechanisms whereby alcohol may increase risk of breast cancer remain uncertain. Alcohol is metabolised hepatically and can influence the functional state of the liver and its ability to metabolise other nutrients, non-nutritive dietary factors and many host *hormones*. Thus, the potential mechanisms affecting breast *carcinogenesis* are diverse. Alcohol can also be metabolised in breast tissue to acetaldehyde, producing reactive oxygen species associated with DNA damage [3]. Alcohol may increase circulating levels of oestrogen, which is an established risk factor for breast cancer [159]. Alcohol may also act as a solvent, potentially enhancing the penetration of carcinogens into cells, which may be particularly relevant to tissues exposed to alcohol. People who consume large amounts of alcohol may have diets deficient in essential nutrients such as folate, rendering breast tissue susceptible to carcinogenesis.

Stomach

The mechanisms that underlie the association between alcohol consumption and stomach cancer development are not well delineated. Alcohol consumption leads to exposure to acetaldehyde, the major and most toxic metabolite of alcohol. Acetaldehyde has been shown to dysregulate DNA synthesis and repair [92]. Exposure to ethanol may also induce oxidative stress through increased production of reactive oxygen species, which are genotoxic and carcinogenic [94]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (for example tobacco) *carcinogens*, affect *hormone* metabolism, or interfere with retinoid metabolism and with DNA repair mechanisms [95].

Breast (premenopause)

The mechanism or mechanisms whereby alcohol may increase risk of breast cancer remain uncertain. Alcohol is metabolised hepatically and can influence the functional state of the liver and its ability to metabolise other nutrients, non-nutritive dietary factors and many host *hormones*. Thus, the potential mechanisms affecting breast *carcinogenesis* are diverse. Alcohol can also be metabolised in breast tissue to acetaldehyde, producing reactive oxygen species associated with DNA damage [3]. Alcohol may increase circulating levels of oestrogen, which is an established risk factor for breast cancer [159]. Alcohol may also act as a solvent, potentially enhancing penetration of *carcinogens* into cells, which may be particularly relevant to tissues exposed to alcohol. People who consume large amounts of alcohol may have diets deficient in essential nutrients such as folate, rendering breast tissue susceptible to carcinogenesis.

Lung

There is limited, though suggestive, evidence that consumption of alcoholic drinks increases the risk of lung cancer. While a biological mechanism or mechanisms that specifically links alcohol drinking with lung cancer has not been established, alcoholic beverages comprise several *carcinogenic* compounds such as ethanol, acetaldehyde and ethyl carbamate, which may contribute to lung cancer development. Acetaldehyde, the first metabolite of ethanol, which is formed by metabolic activity of human cells as well as those of the microbiota, has been classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC). The biological mechanisms by which alcohol intake may increase the risk of lung cancer are likely to include a genotoxic effect of acetaldehyde, alterations in endocrine and growth factor networks, oxidative stress, a role as a solvent for tobacco carcinogens, changes in folate metabolism, and an impact on DNA repair [92, 94, 95].

Pancreas

The underlying mechanisms for the cancer-promoting effects of alcohol are likely to be shared across cancer sites, including the pancreas. These potential mechanisms include induction of oxidative stress through increased production of reactive oxygen species, which are genotoxic and carcinogenic; exposure to acetaldehyde, the carcinogenic metabolite of alcohol metabolism; acting as a solvent for cellular penetration of carcinogens; affecting *hormone* metabolism; interfering with retinoid metabolism and with DNA repair mechanisms [94, 95]. *Chronic* alcohol abuse has been linked to the development of pancreatitis, a major inflammatory condition and risk factor for pancreatic cancer [190].

Skin

The mechanisms of action for an effect of *chronic* alcohol consumption on the development of malignant *melanoma* are not well elucidated. Acetaldehyde, a highly toxic metabolite of ethanol oxidation, can interfere with DNA synthesis and repair, which may result in the development of cancer. Higher ethanol consumption can also induce oxidative stress through increased production of reactive oxygen species, which are genotoxic and carcinogenic [94]. Alcohol may also affect *hormone* metabolism or interfere with retinoid metabolism and with DNA repair mechanisms [95]. Limited experimental evidence in animal models suggests that the consumption of alcohol stimulates melanoma angiogenesis and tumour progression [191].

Kidney

The mechanisms that may explain the inverse relationship between moderate alcohol consumption and kidney cancer risk are uncertain but appear to be consistent for the various renal cancer subtypes [186]. Possible biological mechanisms proposed include improved blood lipid profiles among people who drink a moderate amount of alcohol and higher adiponectin levels [187, 188]. It has been suggested that the diuretic effects of alcohol may, in part, be responsible for lower kidney cancer risk among people who drink alcohol. However, inconsistent results for the consumption of other fluids and of diuretics and kidney cancer risk do not support this hypothesis [189].

Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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